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## Low-dose, long-term macrolide therapy in asthma: An overview

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### Abstract

Macrolides, a class of antimicrobials isolated from *Streptomyces* more than 50 years ago, are used extensively to treat sinopulmonary infections in humans. In addition, a growing body of experimental and clinical evidence indicates that long-term (years), low (sub-antimicrobial)-dose 14- and 15-membered ring macrolide antibiotics, such as erythromycin, clarithromycin, roxithromycin and azithromycin, express immunomodulatory and tissue reparative effects that are distinct from their anti-infective properties. These salutary effects are operative in various lung disorders, including diffuse panbronchiolitis, cystic fibrosis, persistent chronic rhinosinusitis, nasal polyposis, bronchiectasis, asthma and cryptogenic organizing pneumonia.

The purpose of this overview is to outline the immunomodulatory effects of macrolide antibiotics in patients with asthma.

### Macrolide antibiotics and asthma pathogenesis

Asthma is a chronic inflammatory disease characterized by airway narrowing. There are three distinct components of reduction in airway caliber: secretions, smooth muscle contraction and airway wall thickening. While pathogenetic changes that bring about airway narrowing may be heterogeneous, it is generally accepted that inflammatory cell infiltration with secretion of pro-inflammatory cytokines plays a major role in pathogenesis of asthma. The major inflammatory cells that are involved in this process are type 2 helper T (Th2) cells, eosinophils and mast cells.

Upon stimulation, Th2 cells elaborate various cytokines (IL-4, IL-5, IL-13 and GM-CSF in particular) that stimulate the plasma cells to switch to specific IgE production and induce myeloid differentiation. IgE bind to mast cells that

result in secretion of preformed mediators of bronchoconstriction and glandular secretion (histamine, leukotrienes and kallikrein) as well as secretion of cytokines (IL-4 and IL-5), which increase eosinophil chemotaxis and Th2 and mast cell proliferation (positive feedback). When stimulated by IgE, eosinophils release a number of compounds cytotoxic to airway epithelium such as eosinophil cationic protein (ECP) as well as IL-8, a chemotactic factor for eosinophils and neutrophils. Neutrophilic inflammation becomes more pronounced and is related to airflow obstruction particularly in the airways of chronic asthmatics.

The airway epithelium may also play an important role in initiation and maintenance of the inflammatory response through secretion of chemokines such as Regulated on Activation, Normal T-cell Expressed and Secreted

(RANTES) that attracts eosinophils, basophils and lymphocytes to the airway. Airway epithelium also elaborates nitric oxide (NO), which is thought to suppress Th1 cells thereby augmenting Th2 cell induced inflammation. Through a process termed airway remodeling, these acute inflammatory events may lead to cellular proliferation, smooth muscle hypertrophy and hyperplasia, and collagen deposition below the basement membrane. The precise relationship of acute inflammatory cascade to airway remodeling and its modification by host and environmental factors are under investigation.

The 14- and 15-membered ring macrolide antibiotics may interfere with cytokine production and inflammatory cell metabolism relevant to asthma pathogenesis outlined above at various levels. The hydrophobic nature of the 14- or 15-membered lactone ring and hydrophilic nature of both sugar moieties may lead to formation of drug micelles and promote the interaction of macrolide antibiotics with phospholipids in the plasma and intracellular organellar membranes. This, in turn, may alter the biophysical properties of the effector inflammatory cell membrane thereby interfering with the regulation of intracellular metabolic and transcriptional pathways involved in the inflammatory cascade, such as elaboration of reactive oxygen species by NADPH oxidase and release of myeloperoxidase and elastase in neutrophils. This so-called membrane stabilizing effect may in part account for anti-inflammatory actions of macrolide antibiotics [1]. Macrolide antibiotics affect metabolism of various inflammatory mediators. Administration of erythromycin to rats for 3 months reduced production of cytokine induced neutrophil chemoattractant (CINC)-1, rat counterpart for human interleukin-8, from rat alveolar macrophages [2].

Kohayama et al [3] showed a reduction in interleukin-8 release from eosinophils from atopic individuals who were treated with 14-membered ring macrolide antibiotics. In an elegant study probing mechanism of action of this effect, Abe et al [4] investigated the effects of clarithromycin on interleukin-8 gene expression and protein levels in human bronchial epithelial cell line BET-1A. Clarithromycin inhibited IL-8 gene expression in a dose and time dependent manner and the action was mediated by suppression of activated protein-1 binding and nuclear factor (NF)- $\kappa$ B sites. Eosinophil apoptosis is facilitated by macrolides [5]. Erythromycin inhibits RANTES secretion from human fibroblasts in vitro [6]. Macrolides also may reduce GM-CSF secretion from human monocytes and lung fibroblasts [7,8].

Oxidative burst in neutrophils is inhibited by roxithromycin [9]. Shimizu et al [10] showed reduction in expression of messenger RNA for the gene responsible for mucin pro-

duction (MUC5AC) in nasal epithelium of rats administered clarithromycin, inferring a direct inhibitory effect on mucus secretion. Roxithromycin inhibits mast cell inflammatory cytokine production (TNF-alpha) in a dose dependent fashion [11]. In a study of 15 patients with mild to moderate asthma, Chu et al demonstrated reduction of airway edema on endobronchial biopsies, as inferred by relative increase in vascularity, following a 6-week treatment with clarithromycin [12]. Although mechanism of such an effect was unclear, the reduction of edema was significantly more in asthmatic patients who tested positive for *Mycoplasma pneumoniae*, suggesting an antimicrobial mechanism of action. Finally, NO generation in mice in response to lipopolysaccharide stimulation is suppressed significantly after 4 weeks of oral macrolide antibiotic administration, suggesting that anti-inflammatory effects may, in part be mediated by the NO pathway [13].

### **Macrolide antibiotics and asthma therapy**

Macrolide antibiotics, particularly troleandomycin and erythromycin, decrease corticosteroid requirements in patients with prednisolone-dependent asthma. Spector and his colleagues [14] conducted a double-blind crossover trial comparing troleandomycin to placebo in 74 corticosteroid-dependent patients with severe asthma and chronic bronchitis. Two-thirds of patients showed marked improvement in sputum production, pulmonary function measurements, need for bronchodilators, and subjective evaluation. Much of this effect, however, was attributed to troleandomycin-induced inhibition of methylprednisolone and theophylline metabolism by the hepatic cytochrome P-450 complex [15]. Troleandomycin was later discontinued because of its intolerable adverse effects, particularly osteoporosis, associated with prolongation of methylprednisolone half-life and long-term elaboration of prednisone in vivo.

Low-dose, long-term macrolide antibiotics therapy may have effects beyond their corticosteroid-sparing action in asthma. To this end, macrolide antibiotics inhibit lymphocyte proliferation in response to phytohemagglutinin, decrease neutrophil accumulation via decrease in chemotactic activity, decrease mucus secretion and decrease contraction of isolated bronchial tissue [16]. Open label studies with troleandomycin in methylprednisolone-dependent patients with asthma have demonstrated greater reduction in methylprednisolone doses than would have been predicted by inhibition of methylprednisolone metabolism in the liver [17]. Gotfried and his colleagues [18] showed a significant improvement in pulmonary function test results and in quality of life measures in prednisone dependent patients with asthma following a six-week course of clarithromycin without any change of prednisone requirements. In a small case series

of patients administered clarithromycin for one year, two of three prednisone dependent patients were able to discontinue prednisone altogether [19].

Macrolide antibiotics are efficacious in patients with asthma not treated with corticosteroids by reducing airway hyperreactivity and eosinophilic inflammation. A 10-week course of low-dose erythromycin was associated with significant decrease in bronchial hyperresponsiveness to histamine challenge, expressed as PC20, in patients with asthma [20]. In a double blind, placebo-controlled crossover trial, Amayasu et al [21] treated 17 adults with mild to moderate asthma who were clinically stable with low-dose clarithromycin for 8 weeks. Determination of blood and sputum eosinophil counts, sputum eosinophil cationic protein (ECP) levels, and methacholine challenge testing were carried out before and after treatment. At the conclusion of the study, all inflammatory indices and values of PC20 for methacholine improved. In a study of 11 patients with mild asthma, 250 mg azithromycin orally given twice weekly for 8 weeks increased PC20 of methacholine significantly while FEV<sub>1</sub> and FVC did not change [22].

Tamaoki and his colleagues [23] showed that erythromycin, roxithromycin, and erythromycin attenuated the contractile response of human isolated bronchial strips to electrical field stimulation. Macrolide antibiotics may also improve sputum quality and favorably impact secretion clearance in asthma. Rubin and his colleagues [24] showed that treatment with clarithromycin for two weeks improved nasal secretion rheology, hydration, cohesion and transportability in patients with purulent rhinitis. Clarithromycin reduced mucus volume in both patients and healthy individuals.

### Persistent airway infection in asthma and macrolide antibiotics

One possible explanation for the efficacy of low-dose, long-term macrolide antibiotics therapy in patients with asthma is the putative role played by persistent airway infections in its pathogenesis, particularly *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infections [25,26]. These infectious agents may underlie acute asthma exacerbations and the initiation and maintenance of asthma in previously asymptomatic patients [27]. Infection with *Mycoplasma pneumoniae* induces RANTES expression in cultured human airway epithelial cell, an effect that is mitigated with erythromycin [28].

In a randomized double-blind placebo-controlled trial, Kraft and her colleagues [29] studied the effects of low-dose clarithromycin on 52 patients with stable asthma. Patients had baseline spirometry, bronchoscopy with lavage and biopsy for PCR testing for infection with *Chlamy-*

*dia pneumoniae* and *Mycoplasma pneumoniae* and measurement of various inflammatory mediators obtained from the lower respiratory tract. After 6 weeks of treatment with clarithromycin, lung function (FEV<sub>1</sub>) significantly improved but only in the group of patients with evidence of infection. There were also significant reductions in levels of IL-5, IL-12, TNF- $\alpha$  in bronchoalveolar lavage fluid and level of TNF- $\alpha$  in airway tissue in patients with infection. Notably, there was a decrease in TNF- $\alpha$  level in lavage fluid and airway tissue in patients without evidence of infection as well.

These findings were also supported by Black and his colleagues [30] who found that patients with asthma and serological evidence of infection with *Chlamydia pneumoniae* showed improvement in peak expiratory flow rates after a 3-month course of roxithromycin. Intriguingly, the authors also noted that the benefits seemed to diminish at subsequent 3 month and 6 month time points following therapy. They postulated that this was related, in part, to lack of power of the study to detect a difference or failure to eradicate the organisms. Alternatively, the immunomodulatory effects of roxithromycin may have been lost once the drug was stopped. A similar phenomenon was reported in patients with diffuse panbronchiolitis in Japan.

### Conclusions

Low-dose, long-term 14- and 15-membered ring macrolide antibiotic therapy represents a promising addition to our anti-asthma drug armamentarium. The salutary effects of these drugs are related, most likely, to their distinct immunomodulatory properties although eradication of persistent airway infection with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in patients with asthma may also play a role. Clearly, additional, multi-center, randomized, double-blind, placebo-controlled trials are indicated to address these issues.

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