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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 Streptomycetes 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)-κB 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 production (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_1 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 *Chlamydia 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_1) 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-α in bronchoalveolar lavage fluid and level of TNF-α in airway tissue in patients with infection. Notably, there was a decrease in TNF-α 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, multicenter, randomized, double-blind, placebo-controlled trials are indicated to address these issues.

References

1. Garey KW, Alwani A, Danziger LH, Rubinstein IR: **Tissue reparative effects of macrolide antibiotics in chronic inflammatory sinopulmonary diseases.** *Chest* 2003, **123:**261-265.
2. Sugiyama Y, Yanagisawa K, Tominaga SI, Kitamura S: **Effects of long-term administration of erythromycin on cytokine production in rat alveolar macrophages.** *Eur Respir J* 1999, **14:**1113-1116.
3. Kohyama T, Takizawa H, Kawasaki S, Akiyama N, Sato M, Ito K: **Fourteen member macrolides inhibit interleukin-8 release by human eosinophils from atopic donors.** *Antimicrob Agents Chemother* 1999, **43:**907-911.
4. Abe S, Nakamura H, Inoue S, Takeda H, Saito H, Kato S, Mukaida N, Matsushima K, Tomoike H: **Interleukin-8 gene repression by clarithromycin is mediated by the activator protein-1 binding site in human bronchial epithelial cells.** *Am J Respir Cell Mol Biol* 2000, **22:**51-60.
5. Adachi T, Motojima S, Hirata A, Fukuda T, Kihara N, Kosaku A, Ohtake H, Makino S: **Eosinophil apoptosis caused by theophylline, glucocorticoids, and macrolides after stimulation with IL-5.** *J Allergy Clin Immunol* 1996, **98:**S207-S215.

6. Sato E, Nelson DK, Koyama S, Hoyt JC, Robbins RA: **Erythromycin modulates eosinophil chemotactic cytokine production by human lung fibroblasts in vitro.** *Antimicrob Agents Chemother* 2001, **45:**401-406.
7. Morikawa K, Watabe H, Arake M, Morikawa S: **Modulatory effects of antibiotics on cytokine production by human monocytes in vitro.** *Antimicrob Agents Chemother* 1996, **40:**1366-70.
8. Kamoi H, Kurihara N, Fujiwara H, Hirata K, Takeda T: **The macrolide antibacterial roxithromycin reduces bronchial hyperresponsiveness and superoxide anion production by polymorphonuclear leukocytes in patients with asthma.** *J Asthma* 1995, **32:**191-197.
9. Cazzola M, Salzillo A, Diamare F: **Potential role of macrolides in the treatment of asthma.** *Monaldi Arch Chest Dis* 2000, **55:**231-236.
10. Shimizu T, Shimizu S, Hattori R, Gabazza EC, Majima Y: **In vivo and in vitro effects of macrolide antibiotics on mucus secretion in airway epithelial cells.** *Am J Respir Crit Care Med* 2003, **168:**581-587.
11. Shimane T, Asano K, Mizutani T, Suzaki H: **Inhibitory action of roxithromycin on tumour necrosis factor-alpha production from mast cells in vitro.** In *Vivo* 1999, **13:**503-506.
12. Chu HW, Kraft M, Rex M, Martin R: **Evaluation of blood vessels and edema in the airways of asthma patients: Regulation with clarithromycin treatment.** *Chest* 2001, **120:**416-422.
13. Terao H, Asano K, Kanai K, Kyo Y, Watanabe S, Hisamitsu T, Suzaki H: **Suppressive activity of macrolide antibiotics on nitric oxide production by lipopolysaccharide stimulation in mice.** *Mediators Inflamm* 2003, **12:**195-202.
14. Spector S, Katz F, Farr R: **Troleandomycin: effectiveness in steroid dependent asthma and bronchitis.** *J Allergy Clin Immunol* 1974, **54:**367-379.
15. Weinberger M, Hudgel D, Spector S, Chisey C: **Inhibition of theophylline clearance by troleandomycin.** *J Allergy Clin Immunol* 1977, **59:**228-231.
16. Black PN: **Anti-inflammatory effects of macrolide antibiotics.** *Eur Respir J* 1997, **10:**971-972.
17. Rosenberg SM, Gerhard H, Grunstein MM: **Use of TAO without methylprednisolone in the treatment of severe asthma.** *Chest* 1991, **100:**849-850.
18. Gotfried MH Jr, Messick C, Rubinstein IR: **Placebo-controlled trial evaluating the efficacy of clarithromycin in subjects with corticosteroid dependent asthma.** *Birmingham, UK: 21st international Congress of chemotherapy* 1999.
19. Garey KW, Rubinstein I, Gotfried MH, Khan IJ, Varma S, Danziger LH: **Long-term clarithromycin decreases prednisone requirements in elderly patients with prednisone dependent asthma.** *Chest* 2000, **118:**1826-1827.
20. Miyatake H, Taki F, Taniguchi H, Suzuki R, Takagi K, Satake T: **Erythromycin reduces the severity of bronchial hyperresponsiveness in asthma.** *Chest* 1991, **99:**670-673.
21. Amayasu H, Yoshida S, Ebana S, Yamamoto Y, Nishikawa T, Shoji T, Nakagawa H, Hasegawa H, Nakabayashi M, Ishizaki Y: **Clarithromycin suppresses bronchial hyperresponsiveness associated with eosinophilic inflammation in patients with asthma.** *Ann Allergy Asthma Immunol* 2000, **84:**594-598.
22. Ekici A, Ekici M, Erdemoglu AK: **Effect of azithromycin on the severity of bronchial hyperresponsiveness in patients with mild asthma.** *J Asthma* 2002, **39(2):**181-185.
23. Tamaoki J, Tagaya E, Sakai A: **Effects of macrolide antibiotics on neurally mediated contraction of human isolated bronchus.** *J Allergy Clin Immunol* 1995, **95:**853-859.
24. Rubin BK, Druce H, Ramirez OE, Palmer R: **Effect of clarithromycin on nasal mucus properties in healthy subjects and inpatients with purulent rhinitis.** *Am J Respir Crit Care Med* 1997, **155:**2018-2023.
25. Hahn DL: **Chlamydia pneumoniae and asthma.** *Thorax* 1998, **53:**1095-1096.
26. Seggev JS, Lis I, Siman-Tov R, Gutman R, Abu-Samara H, Schey G, Naot Y: **Mycoplasma pneumoniae is a frequent cause of exacerbation of bronchial asthma in adults.** *Ann Allergy* 1986, **57:**262-265.
27. Hahn DL: **Chlamydia pneumoniae, asthma, and COPD: what is the evidence?** *Ann Allergy Asthma Immunol* 1999, **83:**271-288.
28. Dakhama A, Kraft M, Martin R, Gelfand EW: **Induction of regulated upon activation, normal T-cells expressed and secreted (RANTES) and transforming growth factor-β1 in airway epithelial cells by *Mycoplasma pneumoniae*.** *Am J Respir Cell Mol Biol* 2003, **29:**344-351.
29. Kraft M, Cassell G, Pak J: ***Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in asthma: Effect of clarithromycin.** *Chest* 2002, **121:**1782-1788.
30. Black PN, Blasi F, Jenkins CR: **Trial of roxithromycin in subjects with asthma and serological evidence of infection with *Chlamydia pneumoniae*.** *Am J Respir Crit Care Med* 2001, **164:**536-541.