Tissue Reparative Effects of Macrolide Antibiotics in Chronic Inflammatory Sinopulmonary Diseases*

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It is well established that macrolide antibiotics are efficacious in treating sinopulmonary infections in humans. However, a growing body of experimental and clinical evidence indicates that they also express distinct salutary effects that promote and sustain the reparative process in the chronically inflamed upper and lower respiratory tract. Unlike the anti-infective properties, these distinct effects are manifested at lower doses, usually after a relatively prolonged period (weeks) of treatment, and in the absence of an identifiable, viable pathogen. Long-term, low-dose administration of macrolide antibiotics has been used most commonly for sinusitis, diffuse panbronchiolitis, asthma, bronchiectasis, and cystic fibrosis. It is associated with down-regulation of nonspecific host inflammatory response to injury and promotion of tissue repair. Although large-scale trials are lacking, the prolonged use of these drugs has not been associated with emergence of clinically significant bacterial resistance or immunosuppression. Long-term, low-dose administration of 14- and 15-membered ring macrolide antibiotics may represent an important adjunct in the treatment of chronic inflammatory sinopulmonary diseases in humans. (CHEST 2003; 123:261–265)

Key words: anti-inflammatory; immunomodulatory; macrolide antibiotics

Abbreviation: IL = interleukin

It is well established that macrolide antibiotics, including the semisynthetic derivatives of erythromycin, are clinically useful in treating sinopulmonary infections in humans.1–3 However, a growing body of experimental and clinical evidence emanating predominantly from Japan indicates that the 14- and 15-membered ring macrolide antibiotics also possess distinct salutary properties that promote and sustain the reparative process in the chronically inflamed upper and lower respiratory tract.4,5 Unlike the anti-infective properties, these distinct effects are expressed at lower doses, usually after a relatively prolonged period (weeks) of treatment, and in the absence of an identifiable, viable pathogen.4,6–8 Importantly, long-term, low-dose administration of 14- and 15-membered ring macrolide antibiotics is not associated with increased incidence of adverse events, emergence of clinically relevant bacterial resistance, or immunosuppression.5,8–10

Although the mechanisms underlying the pleiotropic tissue reparative effects of macrolide antibiotics in chronically inflamed sinopulmonary tissues in humans are uncertain, they may be related, in part, to the highly hydrophobic nature of the 14- and 15-membered lactone ring coupled with the hydrophilic nature of both sugar moieties of the cell.4,11–13
This distinct biophysical feature may form drug micelles and promote avid and preferential interaction of macrolide antibiotics with phospholipids in the plasma and intracellular organellar membranes, including the nucleus, in activated effector cells that sustain uncontrolled, self-perpetuating inflammation in the chronically inflamed sinopulmonary tissue, such as leukocytes, macrophages, epithelial cells, goblet cells, and fibroblasts. \(^3\) This process may, in turn, alter the biophysical state of the membrane bilayer in effector cells, including fluidity and charge, thereby disrupting the functional integrity of key membrane-associated proteins that regulate key intracellular metabolic and transcriptional pathways involved in the inflammatory cascade, such as reactive oxygen species, nitric oxide, and cytokines.\(^13\)–\(^15\)

The purpose of this review is to provide a concise account of the tissue reparative effects of macrolide antibiotics in chronic inflammatory sinopulmonary diseases in humans based on published English-language literature. Articles were identified by a MEDLINE search from 1966 to present using the search terms macrolides, anti-inflammatory, and immunomodulatory, and a review of identified bibliographies. A detailed account of the putative cellular and molecular mechanisms underlying these effects is beyond the scope of this article.

**Chronic Inflammatory Sinopulmonary Diseases**

**Chronic Rhinosinusitis and Nasal Polyps**

Chronic sinusitis, a common disease of the paranasal sinuses, is characterized by purulent sinus effusion and nasal discharge.\(^16\) Neutrophils play an important role in regulating the inflammatory process by secreting various pro-inflammatory cytokines, such as interleukin (IL)-8.\(^17\) Fourteen-membered ring macrolide antibiotics, such as erythromycin and clarithromycin, are efficacious in chronic sinusitis.\(^8\)–\(^10\) Patients administered low-dose clarithromycin\(^8\) or roxithromycin (not available in the United States)\(^10\) displayed improved aeration, and decreased neutrophil and IL-8 levels in the nasal discharge. Suzuki et al\(^21\) determined the prognostic factors that influence the efficacy of low-dose macrolide antibiotic therapy. They found that patients without atopy or eosinophilia were more likely to respond to either clarithromycin or roxithromycin. Importantly, maximal effects were not seen until at least 12 weeks of continuous therapy, and the authors hypothesized that even longer treatment may be necessary for maximal effect. In further *in vitro* studies, cultured nasal epithelial cells from patients with chronic sinusitis secreted less IL-8 in the presence of low concentrations of 14-membered ring macrolides.\(^19\)–\(^22\)–\(^24\)

**Asthma**

Macrolide antibiotics, especially troleandomycin and erythromycin, have been studied since the 1950s and have been shown to decrease corticosteroid requirement in patients with corticosteroid-dependent asthma.\(^25\)–\(^27\) For instance, Spector et al\(^28\) reported a double-blind, crossover trial comparing troleandomycin to placebo in 74 corticosteroid-dependent patients with severe asthma and chronic bronchitis. Sixty-seven percent of patients had a marked improvement in sputum production, pulmonary function measurements, need for bronchodilators, and subjective evaluations. Much of this effect, however, was attributed to troleandomycin-induced inhibition of methylprednisolone and theophylline metabolism by the hepatic cytochrome P450 complex.\(^29\)–\(^32\)

*In vitro* studies have suggested that macrolide antibiotics have beneficial anti-inflammatory and immunomodulatory effects in patients with asthma who are independent of the corticosteroid metabolism.\(^33\) Macrolide antibiotics inhibit lymphocyte proliferation in response to phytohemagglutinin, decrease neutrophil accumulation through decrease chemotactic activity, decreased mucus secretion, and decrease contraction of isolated bronchial tissue.\(^34\)

Open-label studies with troleandomycin in methyprednisolone-dependent patients with asthma (adults and children) have demonstrated greater reduction in corticosteroid doses than would be predicted by hepatic inhibition of corticosteroid metabolism.\(^27\)–\(^35\) Gotfried et al\(^36\) showed a significant improvement in pulmonary function test results and quality of life measures in prednisone-dependent patients with asthma administered a 6-week course of clarithromycin without any change in prednisone requirements. In a small case series of patients administered clarithromycin for 1 year, two of three prednisone-dependent patients were able to discontinue prednisone entirely.\(^10\)

Macrolide antibiotics are efficacious measures in asthmatic patients without corticosteroid dependency by reducing airway hyperreactivity.\(^31\)–\(^37\)–\(^41\) A 10-week course of low-dose erythromycin was associated with a significant decrease in bronchial hyper-responsiveness in asthmatic patients tested by histamine challenge.\(^38\)–\(^39\) Similar effects were observed when 12 hospitalized children were treated with roxithromycin.\(^42\) Tamaoki et al\(^43\) showed that erythromycin, roxithromycin, and clarithromycin attenuated the contractile response of human isolated bronchial strips to electrical field stimulation. They
hypothesized that macrolide antibiotics inhibit the cholinergic neuroeffecter transmission in human airway smooth muscle.

Another possible explanation for the efficacy of macrolide antibiotics in patients with asthma is the role of chronic infectious diseases, particularly *Chlamydia pneumoniae*. These infectious agents may underlie acute asthma exacerbations and the initiation and maintenance of asthma in previously asymptomatic patients. The anti-infective vs tissue reparatory effects of macrolide antibiotics in asthma will require further controlled studies to unravel these pathways.

**Diffuse Panbronchiolitis**

Diffuse panbronchiolitis, a noninfectious, inflammatory disease prevalent in Japan, is characterized by chronic inflammation of the respiratory bronchiolones, and parabronchial and luminal accumulation of mononuclear inflammatory cells. Persistent accumulation of neutrophils evokes airway damage through the effects of oxidative and proteolytic products. In addition, there is a significant correlation between neutrophil accumulation and augmented neutrophil chemotactic activity in the BAL fluid of these patients. Diffuse panbronchiolitis presents with chronic cough, mucopurulent expectoration, and dyspnea, and is associated with chronic sinusitis in 75% of cases. The chest radiograph and high-resolution CT findings reveal diffuse ill-defined centrilobular nodules with hyperinflated lungs. Bronchiectasis is observed in the most advanced cases. Infections with *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumonia*, and *Staphylococcus aureus* are common and are ultimately superceded by infections with *Pseudomonas aeruginosa*. Untreated, the 5-year mortality rate is 50% and the 10-year survival rate is 25%. Kudoh reported that long-term, low-dose oral administration of erythromycin was effective in the treatment of diffuse panbronchiolitis. Eighteen patients with diffuse panbronchiolitis were treated for 19 months with significant increases in lung function along with decreased signs and symptoms of disease. Similar effects were observed with roxithromycin, clarithromycin, and azithromycin. Clindamycin, piperacillin, and ampicillin, administered as comparator agents in these trials, were ineffective. Since the initiation of macrolide antibiotic therapy in patients with diffuse panbronchiolitis, the 10-year survival rate has improved > 90%. However, the mechanisms underlying these salutary effects have not yet been elucidated.

**Non-Cystic Fibrosis Bronchiectasis and Chronic Bronchitis**

Bronchiectasis and chronic bronchitis are characterized by excessive mucus production. An 8-week pilot study of low-dose erythromycin showed an improvement in lung function and a decrease in sputum volume in patients with bronchiectasis. Koh et al treated 25 children with bronchiectasis with 12 weeks of low-dose roxithromycin and found an improvement in sputum purulence by 6 weeks and a decrease in airway hyperresponsiveness by inhaled methacholine challenge. In another study, low-dose roxithromycin treatment improved symptoms, pulmonary functions, and radiographic findings of patients with chronic lower respiratory tract inflammation. This was associated with a decrease in IL-8, neutrophil elastase, and complement 5a concentrations in the epithelial lining fluid and resulted in attenuation of neutrophil infiltration.

**Cystic Fibrosis and P aeruginosa Colonization**

Nonmucoid *P aeruginosa* initially invades the airway of patients with cystic fibrosis and subsequently transforms into mucoid strains producing alginate, a major component of the mucoid material. These mucoid strains form a bacterial biofilm by encasing the alginate around them as they adhere to the airway mucosa, thereby enhancing their resistance to the host’s phagocytic activity. Alginate also increases sputum viscosity thus promoting bacterial colonization.

The minimum inhibitory concentration of macrolide antibiotics for most pseudomonal infections is higher than the peak serum concentration achieved after the IV administration of these drugs. Thus, by conventional criteria, *P aeruginosa* is resistant to macrolide antibiotics. However, Kita et al showed that erythromycin exhibited an inhibitory effect on the virulence factors produced by *P aeruginosa*, such as protease, elastase, and leucocidin. Likewise, 14- and 15-membered ring macrolide antibiotics inhibit alginate production by mucoid *P aeruginosa* strains, an effect not seen with 16-membered ring macrolide antibiotics. It is also notable that 14- and 15-membered ring macrolide antibiotics can facilitate the penetration of bacterial biofilm by ciprofloxacin thus eliminating bacteria inside the biofilm.

**Cryptogenic Organizing Pneumonia**

Hotta showed that in a small number of patients with cryptogenic organizing pneumonia, daily, low-dose, oral erythromycin for 2 to 3 months is associated with a favorable clinical response along with a significant decrease in IL-8 and neutrophil chemo-
tactic activity in the BAL fluid. These preliminary observations should be corroborated by large-scale studies using well-defined patient populations with idiopathic pulmonary fibrosis.

**CONCLUSION**

Long-term, low-dose administration of 14- and 15-membered ring macrolide antibiotics is associated with salutary tissue reparative effects in patients with chronic inflammatory sinopulmonary diseases such as chronic sinusitis, asthma, bronchiectasis, cystic fibrosis, and diffuse panbronchiolitis that are distinct from their anti-infective properties. Overall, these responses are associated with down-regulation of clinically significant bacterial resistance or immunosuppression. Large-scale, double-blind, randomized studies are warranted to establish the merit of long-term, low-dose macrolide antibiotic therapy in chronic inflammatory sinopulmonary conditions.

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