Pulmonary Anti-Inflammatory Effects of Macrolides

62

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Contents

Introduction

The aim of this chapter is to present a brief update on the role of macrolides and their anti-inflammatory effect on the lungs, and their efficacy and safety regarding other specific respiratory conditions, such as cystic fibrosis (CF), bronchiectasis, asthma, obliterative bronchiolitis, and sinusitis.

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Macrolides

Macrolides are a complex and wide family of antibiotics derived from the *Streptomyces* family, discovered in the middle of last century, on Philippine soil. They are characterized by the presence of a lactonic ring with at least one amino sugar in their structure. Owing to their strong antibiotic effect on aerobic gram positive, anaerobic, and gram negative bacteria, there are an increasing number of studies revealing their immunomodulatory and anti-inflammatory properties both in children and adults. These drugs do not present a bacteriostatic or bactericide effect against *Pseudomona aeruginosa* almost at all, which is why the idea that there must be a different mechanism for its clinical effect to happen has been a point of discussion.

Macrolides' anti-inflammatory effect was first recorded during simple observations on patients with severe asthma in 1959, when

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Kaplan and Goldin reported that a group of patients with severe asthma—daily steroid users—required a smaller dose of steroids after being administered troleandomycin. Later, in the 1970s, Itkin et al. reported the benefit of administering macrolides, managing to reduce the steroid dose in patients with "infectious asthma." These two anecdotal experiences were the first published "evidence" suggesting a non-antibiotic property of macrolides.

The most convincing demonstration of the anti-inflammatory effect of macrolides on the lung was the treatment of diffuse panbronchiolitis (DBP) carried out in Japan. This disease of unknown origins was first reported by Homme in 1969 as generally initiating symptoms after the fourth decade of life with clinical characteristics similar to cystic fibrosis: Obstructive-restrictive ventilatory pattern, *Pseudomona aeruginosa* colonization, and development of bronchiectasis, and in individuals whose survival rate after 5 years was lower than 30%. A retrospective study of 498 adults suffering from diffuse panbronchiolitis showed that subjects who used erythromycin for different periods presented a significant increase in their survival rate over 10 years of up to 90%, along with reduction in morbidity and improvement in lung function. This effect was clearer in older patients colonized by *P. aeruginosa* who suffered from diffuse panbronchiolitis.

The effectiveness of macrolides as anti-inflammatory agents seems to be limited to members of the lactone 14 and 15 groups, such as erythromycin, clarithromycin, and azithromycin. These drugs have been shown to improve lung function and reduce morbidity and mortality in patients with diffuse panbronchiolitis and cystic fibrosis.

Physiopathology

Many studies have developed interesting hypotheses to explain the immunomodulatory effect displayed by macrolides in different respiratory conditions. There probably is no single mechanism for their action, given that these drugs act across the inflammatory cascade both in vitro and in vivo (Fig. 62.1).

- *Modulation of the inflammatory cascade*. Macrolides inhibit the production and discharge of pro-inflammatory cytokines (IL-1, IL-6, IL-9, and TNFα), both in vitro and in blood samples and bronchoalveolar lavage (BAL) in patients with diffuse panbronchiolitis. It is assumed that the cause of this effect is the inhibition of nuclear factor kappa B (NF-Kb), an essential protein for the transcription of the genes that encode pro-inflammatory molecules like IL-8. This molecule is released as a response to lipopolysaccharides, immune complexes, and other cytokines. IL-8 is a powerful chemotactic factor for neutrophils, eosinophils, and other inflammatory mediators. Generally speaking, macrolides inhibit the expression of the inducible nitric oxide synthase enzyme, reducing the formation of superoxide anions and free radicals, which may have a role in chronic lung conditions where the oxidative factor is prevalent, as in cystic fibrosis.
- *Effect on neutrophils*. Many studies have shown a reduction in neutrophil migration and chemotactic activity after being exposed to macrolides, as they inhibit the formation of cytokines, B4 leukotrienes, and other necessary macromolecules for the adhesion of these cells, such as ICAM. In vitro models show that erythromycin increases the levels of AMPc in neutrophils depending on dosage, accelerating cellular apoptosis with a marked reduction in the number of neutrophils in the sputum.
- *Biofilm*. Permanent (mucoid and non-mucoid) *P. aeruginosa* colonization occurs in around 70% of patients with diffuse panbronchiolitis and around 80% of patients with cystic fibrosis at some point during the disease. This colonization reduces the survival rate of patients as the number of polymorphonuclears and protease in the sputum increases, therefore increasing lung damage. Macrolides modify the virulence of *P. aeruginosa*, reducing the release of elastase, protease, phospholipase,

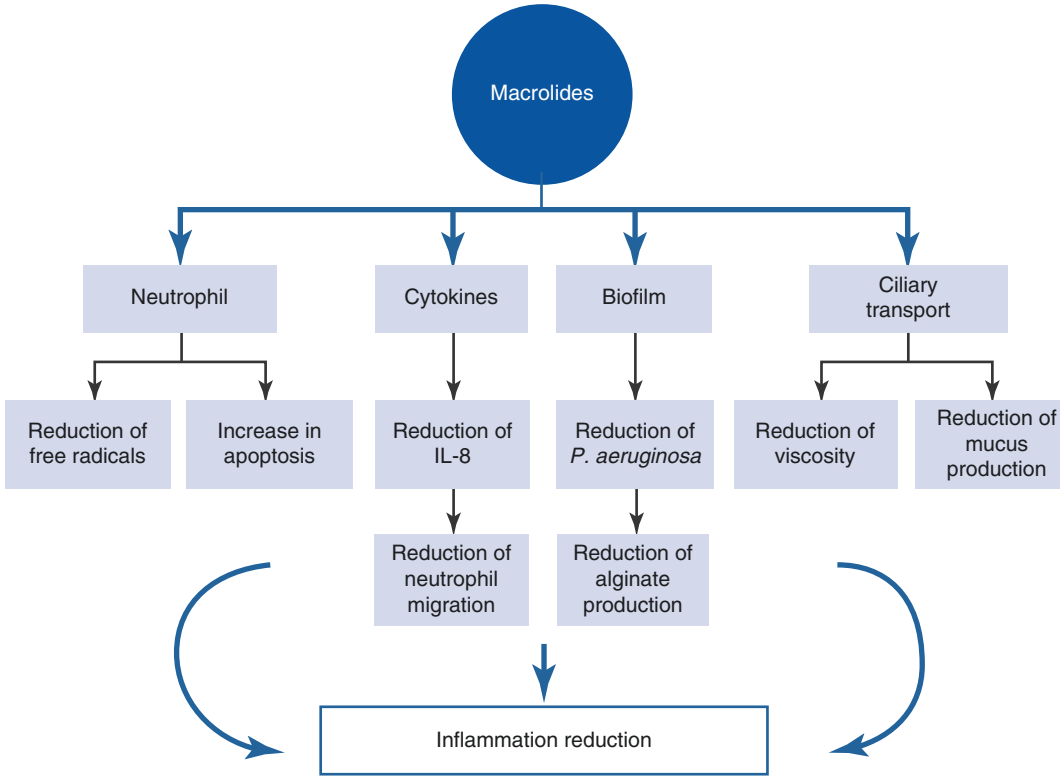

Fig. 62.1 Anti-inflammatory mechanisms of macrolides Macrolides act on neutrophils and reduce the production of free radicals while increasing cellular apoptosis. The stimulation of some cytokines inhibits the release of IL-8. In addition, they reduce the count of colonies of Pseudomona aeruginosa on the mucus biofilm or by increasing ciliary transport and reduction of its viscosity. All these effects together translate into a reduction of the inflammatory cascade in the airway

and exotoxins. Mucoid *P. aeruginosa* produces alginate, forming a biofilm that interferes with the elimination of this bacterium. It behaves like a specific antibody–antigen reaction, inducing antigen on the surface of the airway. Production of alginate has also been reported in other forms of *P. aeruginosa*. Azithromycin reduces serum immune complexes, secondary inflammation, and adherence of *P. aeruginosa* to the respiratory epithelium of the airway. Some randomized and controlled studies in patients with cystic fibrosis have shown that daily treatment with azithromycin for at least 3 months reduces the number of respiratory exacerbations without significantly altering the respiratory flora. This effect becomes clearer in patients infected by *P. aeruginosa*. The doses used are smaller than the minimal inhibitory concentration against this germ, suggesting that its antibacterial effect is not responsible and indicates the presence of a different mechanism. An in vitro study comparing the combination of ciprofloxacin and azithromycin versus ciprofloxacin showed that combined therapy increased the elimination of *P. aeruginosa*, suggesting a higher degree of penetration by the quinolone in the biofilm, favored by the action of the macrolide.

- *Aspects of the mucus*. Macrolides inhibit the expression of genes that produce mucin in the cells of the bronchial epithelium, therefore reducing the production of mucus by goblet cells. In patients with cystic fibrosis colonized by *P. aeruginosa*, macrolides reduce the viscosity of mucus in up to 80% compared to a

placebo, perhaps related to the decrease in production of alginate. Rubin and company compared mucus discharges in healthy patients against those suffering from purulent rhinitis. After 2 weeks of therapy with clarithromycin, a reduction of mucus discharges was observed in both groups, but the group with purulent rhinitis also saw a reduction in viscosity.

- *Bronchoconstriction*. Macrolides reduce the expression of endothelin-1, a powerful natural vasoconstrictor and bronchoconstrictor. An in vitro study showed that administering erythromycin inhibits the contraction of smooth muscle cells of the human bronchial epithelium as a response to the electric stimulus. This action would happen when inhibiting the cholinergic response, because administering acetylcholine blocks this biological effect.

Clinical Effectiveness

- *Cystic fibrosis*. On the basis of the similarities between cystic fibrosis and diffuse panbronchiolitis, a pilot study on children with cystic fibrosis and *P. aeruginosa* infection showed a short-term improvement in lung function with the use of macrolides. Afterward, some controlled studies evaluated the effect of macrolides in the treatment of cystic fibrosis, showing an improvement in FEV_1 of 3.5–5.5% as well as a reduction in the use of antibiotics and the number of respiratory exacerbations. A trial of 185 patients with preliminary data suggested a substantial improvement in lung function in patients who received macrolides chronically. On the other hand, the Cochrane group concluded that the benefits of azithromycin in patients with cystic fibrosis are limited but significant. Similarly, administering nebulized deoxyribonuclease to patients suffering from cystic fibrosis has shown an increase in VEF_1, FVC, as well as a reduction in the number of acute exacerbations attributed to the reduction in the DNA levels of the bronchoalveolar lavage samples.
- *Bronchiectasis*. There is little evidence of the usefulness of macrolides in patients with bronchiectasis not associated with cystic fibrosis. A study did not find any differences in lung function tests when monitoring patients treated with roxithromycin for 12 weeks, but there was a reduction in bronchial hyperresponsiveness (BHR) and an improvement in mucus viscosity in the treated group. Many of these studies conclude that subjects with cystic fibrosis colonized by P. aeruginosa suffer from bronchiectasis, which is why it is hard to isolate the cause of either of the inflammatory components. There are valid reasons to test small-dose long-term plans in subjects able to undergo lung function tests that allow observing and monitoring the response, or, failing this, in those who do not respond to conventional treatments. Some countries in Europe recommend testing nebulized deoxyribonuclease for 2 months in patients who fail a macrolide test.
- *Asthma*. Asthma is the prototypical inflammatory airway disease. Some patients suffering from severe asthma who depend on systemic steroids and have received macrolides are capable of reducing or suppressing steroids without worsening their lung function. Using azithromycin has produced some benefits, despite the fact that it does not interact with the steroid metabolism, thus suggesting direct anti-inflammatory activity of macrolides, which would reduce bronchial hyperactivity. Patients with allergic asthma are able to reduce the levels of IL-8 released by eosinophils in a dose- and time-dependent manner. Low macrolide doses could be systemic steroid ‘savers’ in patients with more severe asthma, either because of lymphocyte proliferation inhibition, reduction in the accumulation of neutrophils, mucus, or contraction of the smooth muscle, because of its direct (inhibitory) action on nuclear factor NF-Kb or because of the induced reduction of eosinophils’ apoptosis. Macrolides are effective in reducing bronchial hyperresponsiveness and eosinophilic inflammation. Amayasu et al. measured bronchoconstriction caused by inhaling methacholine in

17 patients suffering from asthma who received a placebo or 200 mg of clarithromycin twice a day for 8 weeks, with a significant decrease in all inflammatory indexes, symptoms, bronchial hyperresponsiveness, and eosinophil levels within the treated group. A possible explanation for the shown effects is the role that some infections by atypical germs play in the persistence of the airway inflammation. *M. pneumonia* can start or perpetuate an asthma attack in previously healthy or stable subjects. Also, it causes the expression of RANTES in cell cultures, an effect that becomes inhibited after the use of macrolides. The anti-inflammatory effect on asthma of macrolides is widely discussed because of its frequent association with *M. pneumoniae* and *C. pneumoniae*, not only because of the role they play in respiratory exacerbations but also as being responsible for prolonging the inflammatory process. Treatment with macrolides significantly improves FEV_1 in asthmatic patients with positive isolation for *M. pneumoniae* and *C. pneumoniae* through PCR techniques. There also was a reduction in inflammatory mediators, such as IL-5 and IL-12, and in neutrophil and IL-8 released by eosinophils in atopic patients. Most patients require at least 2 months of treatment before showing improvement, and the benefits disappear after suspending macrolide treatment for longer than 3 months. Lacking double-blind peer-reviewed studies it is not possible to recommend the use of macrolides for asthma treatment. Despite the complications in identifying and isolating inflammatory component vs. the infections component (cause-effect), the possibility of infection by atypical bacteria must be considered for patients with asthma who do not respond to the usual dose of inhaled steroids.

- *Obliterative bronchiolitis*. Since the 1980s, bronchiolitis obliterans (OB) has been recognized as a severe complication after lung transplant. Even though its pathogenesis is unknown, there are well identified risk conditions. Diagnosis is usually complex. Khalid et al. evaluated administering 500 mg. of azithromycin for 3 days, followed by 250 mg on alternate days for 12 weeks in 20 adults, observing in this way an improvement in FCV and FEV_1 of 20% and 22%, respectively. Another recent open and unreviewed study evaluated six lung transplant recipients who received azithromycin on alternate days, showing a considerable average improvement in FEV_1 of 17.1% over the base value before treatment. Even though its mechanisms are still unknown, there was good drug tolerance. However, more studies are required to determine the safety and benefit of these therapies.
- *Chronic sinusitis*. Since 1991, many, but mainly Japanese publications, have shown that macrolides, particularly clarithromycin on ~500 mg doses twice a day, produce better mucociliary clearance, a decreased discharge volume, and a reduction in inflammation markers on the mucus of chronic sinusitis patients. Sinus symptoms have been reduced at a rate of 50–100% according to a study using 600 mg/day doses of clarithromycin for 7 months. At the same time, patients suffering from chronic sinusitis and nasal polyposis saw a reduction in the size of their polyps correlated to the degree of IL-8 reduction. Clinical improvement was documented at 5%, 48%, 63%, and 71%, respectively after 2, 4, 8, and 12 weeks of treatment. The authors of the study speculated that the clinical effects they found were secondary to a circulating cytokine release control and their previously reported action on the nasal epithelium. Their long-term recurrence effects after suspending treatment have not been evaluated.

Adverse Effects

In general, new macrolides are well tolerated and most adverse effects are mild. The most common alterations are nausea and diarrhea (6%), dyspepsia, abdominal pain or headaches (1.6%). A minor, but typical, secondary effect of clarithromycin was altered taste in between 9% and 14% of patients. From 1% to 6% of patients have abandoned treatment because of their secondary effects, a similar rate to other antibiotics or placebos. Some aspects

of distribution volume must be considered in patients with cystic fibrosis, as they usually receive higher doses at different intervals than known standards.

On the other hand, patients with cystic fibrosis do not usually metabolize macrolides, so in order to obtain beneficial effects, long treatments are required, which is why the correct dose for this patient subgroup is unknown. Despite the theoretical risk, overusing antibiotics may produce a dangerous increase in bacterial resistance, demanding constant monitoring. Still, the administered immunomodulating doses are small. Finally, yearly monitoring of liver enzymes must be considered for patients with cystic fibrosis who have been administered these drugs.

Limits of the Treatment

It is clear that some patients improve their condition after being exposed to macrolides. Yet, some patients do not. Currently, there is no way to predict the response to this treatment. Beyond sputum bacteriology or bronchoalveolar lavage, their usage must be suspended if there is no clear evidence of response to the treatment. Research is still in progress in this area, and "cut-off points" regarding their potential benefits are still necessary.

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