EDITORIAL

Macrolides: Not Just Antibiotics

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Erythromycin was first used in some asthma patients as far back as 1958.[1] However, it was not until 1980, after the surprising improvement in survival among patients with diffuse panbronchiolitis treated with erythromycin, that the immunomodulatory potential of macrolides began to be discussed.[2] Since then, erythromycin, clarithromycin, roxithromycin, and, particularly, azithromycin have been studied in various diseases, both in vitro and in vivo, in an attempt to demonstrate the anti-inflammatory effects that have been postulated for them.

The macrolides make up a family of antibiotics with a 14-, 15-, or 16-membered lactone ring, to which 1 or more neutral sugars are linked by glycoside bonds.[3] With the exception of azithromycin, they are all metabolized in the liver and use the metabolic pathway of the cytochrome P450 enzyme system; therefore, they can interact with other drugs sharing the same pathway. Azithromycin has a long half-life and maintains high serum concentrations for more than 7 days after the last dose. Macrolides form a reversible bond with the 50S subunit of the bacterial ribosome and inhibit protein synthesis. In broad terms, they are mainly active against gram-positive cocci and rods, but also act against some gram-negative microorganisms (*Haemophilus*, *Moraxella*, and *Campylobacter* species) and intracellular bacteria such as *Mycoplasma, Chlamydia* or *Legionella* species. Although they are not active against *Pseudomonas aeruginosa*, they do show some subinhibitory activity in vitro and after more than 48 hours' exposure.[3,4] Macrolides, especially azithromycin, interfere with quorum sensing, that is, the signaling mechanisms that allow the microorganism to determine bacterial density and that genetically regulate production of virulence factors.[5] They also diminish bacterial adhesion[6] and reduce expression of flagellin, a potent stimulator of inflammation. Azithromycin inhibits the protein synthesis of *P aeruginosa* and reduces the secretion and production of its exoproducts[7]; it also reduces the protective effect of the bacterial biofilm and inhibits the production of alginate, which is necessary for its formation.[4]

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Azithromycin, in particular, reduces the expression of messenger RNA in mucin proteins, thus diminishing the viscoelasticity of the respiratory secretions. Similarly, it inhibits the production of lipopolysaccharides in goblet cells, thereby reducing the volume of secretions and increasing mucociliary transport.[8,9] In cystic fibrosis, macrolides have been observed to restore transmembrane conductance in the airway by increasing the synthesis of messenger RNA in a protein known as the multidrug-resistance protein, which appears to act as a chloride ion pump and to regulate secretion of water into the airway lumen.[10] It has been posited that the anti-inflammatory properties of macrolides stem from their ability to inhibit κB nuclear factor and activating protein-1; this leads to reduced secretion of pro-inflammatory cytokines and chemokines. Similarly, they inhibit the expression of the inducible nitric oxide synthase enzyme and secretion of nitric oxide.[11,12] Another important factor is their ability to accumulate in the neutrophil and interfere in its chemotaxis and migration to the focus of inflammation by regulating cell surface expression of selectins and integrins, and other intracellular and vascular adhesion molecules. Furthermore, they have been shown to favor neutrophil apoptosis and clearance by macrophages.[13,14]

Asthma is a chronic disease of the airways in which inflammation plays an essential role. The mechanisms responsible for maintenance of the inflammatory cascade are only partially known, and there are indications that chronic infection by intracellular pathogens such as *Chlamydia pneumoniae* could play a role in pathogenesis. It may be that macrolides reduce inflammation in the airways of these patients,[15-17] but there is little evidence to support this. There are limitations on the interpretation of available randomized clinical trials because different therapeutic regimens have been used. Likewise, studies have enrolled various types of asthma patient (with varying degrees of severity, aspirin intolerance,[18] dependence on corticosteroids,[19,20] positive *Chlamydia* species serology,[21,22] and allergy-based asthma[23,24]). These 7 well-designed studies included a total of 416 patients who received different macrolides for at least 4 weeks. The results showed an improvement in the scores for nighttime and daytime symptoms in the treatment group, and in 2 of the studies,[23,24] reduced eosinophilia and bronchial hyperresponsiveness were also observed. However, no differences were observed in forced expiratory volume in 1 second (FEV_1) and forced vital capacity, although the

study in *Chlamydia* species-positive patients did show a trend towards improvement.[22]

Diffuse panbronchiolitis, which is prevalent in eastern Asia, is a chronic, progressive disease with onset at around 40 to 50 years of age that manifests with productive cough, wheezing, and dyspnea on exertion. As the disease progresses, bronchiectasis appears and a large number of bacteria—mainly *P aeruginosa*—colonize the airway. Before the systematic use of erythromycin,[25] 50% of patients died within 5 years. A recent review on the use of macrolides in diffuse panbronchiolitis included 18 studies performed between 1989 and 2003; most were retrospective.[26] These covered a total of 900 patients who received low-dose macrolides for more than 2 months. Only 1 study was placebo-controlled.[27] All agreed that macrolides led to clinical and functional improvement, with remarkable survival results.

Cystic fibrosis is a genetic disease caused by the mutation of the cystic fibrosis transmembrane conductance regulator gene, which functions as a chloride ion channel whose alteration leads to an increase in viscous and thick secretions in the affected organs. In the lung, this favors bacterial infection.[4] A 2004 Cochrane Library review on macrolides and cystic fibrosis[28] was able to select 4 out of the 14 articles identified. One was a 2002 study by Equi et al[29] (41 children with cystic fibrosis aged 8 to 18 years who received azithromycin at 250 or 500 mg every 24 hours for 6 months and of whom only 21 were colonized by *P aeruginosa*). The second, by Wolter et al,[30] was also from 2002. Sixty patients with cystic fibrosis aged 18 to 44 received azithromycin at 250 mg every 24 hours for 3 months; almost all the patients were colonized by *P aeruginosa*). In the 2003 study by Saiman,[31] 185 patients, including children aged more than 6 years, received azithromycin at 250 or 500 mg, 3 days a week for 6 months; all the patients were colonized by *P aeruginosa*. Finally, a 2001 study by Cipolli et al[32] enrolled 10 patients with cystic fibrosis to compare the pharmacokinetic results of administering 500 mg or 1 g of azithromycin for 5 days. They all reported a small but significant improvement in respiratory function. Saiman also reported an improvement in body weight and some quality of life parameters. A subsequent report by Saiman et al,[33] in which the results were reanalyzed by subgroup, showed that even those patients with no improvement in lung function presented fewer exacerbations and hospitalizations and reduced use of antibiotics.

Clement et al[34] later carried out a 12-month multicenter double-blind study in which treatment led to a longer exacerbation-free period, although they did not observe an improvement in lung function in the treatment group. A difference between this study and others was that the mean FEV_1 was greater (approximately 85% of that measured).

Underlying the hypothesis of the vicious circle in bronchiectasis is the fact that bacterial colonization of the respiratory tract prolongs inflammatory changes and lung damage. Given the encouraging results obtained with macrolides in patients suffering from diffuse panbronchiolitis and cystic fibrosis, there continues to be growing interest in investigating their potential role in non–cystic fibrosis bronchiectasis. In a double-blind, placebo-controlled trial enrolling 24 adults with bronchiectasis who received a low dose of erythromycin (500 mg every 12 hours) for 8 weeks, Tsang et al[35] observed significant improvements in FEV_1, forced vital capacity, and sputum volume after 24 hours. Koh et al[36] carried out another study with 25 children who received roxithromycin for 12 weeks. No significant improvement in lung function was observed, although there were reductions in hyperresponsiveness, sputum purulence, and leukocyte count. These studies did not provide data on the appearance of resistance after treatment, nor did they determine whether colonization was caused by *P aeruginosa* or not. Davies and Wilson[37] administered azithromycin prophylaxis to 39 patients with bronchiectasis over a period of 4 months. The authors observed significantly fewer exacerbations and an improvement in spirometry findings, although only diffusion improved significantly.

Bronchiolitis obliterans is a fibrogenic inflammatory process in the respiratory bronchiole that causes cicatricial stenosis of the airway and severe bronchial obstruction. Although there are no randomized controlled trials on the use of macrolides in this disease, Yates et al[38] published a case series of patients with bronchiolitis obliterans secondary to transplantation who, after 250 mg of azithromycin every 48 hours, showed improvement —albeit slight—in lung function (110 mL) over a period of 6.25 months. This study is consistent with 3 other case series on the use of azithromycin in patients with bronchiolitis obliterans secondary to lung transplant.[39-41]

Chronic obstructive pulmonary disease is a frequent condition with significant morbidity and mortality characterized by limited airflow that is generally progressive and associated with an inflammatory response in the lung and with frequent bacterial infection. Few studies—some only published as abstracts—analyze the efficacy of macrolides in chronic obstructive pulmonary disease and their results vary.[42,43]

Current guidelines[44,45] recommend macrolides for the treatment of acute lower respiratory tract infection in patients with uncomplicated exacerbations, preserved lung function, a low number of infections per year, and no significant concomitant condition. However, more and more data show that macrolide-containing antibiotic regimens are associated with lower mortality and a shorter hospital stay, perhaps because of their anti-inflammatory properties.[46,47]

The studies analyzed allow us to conclude that 14- and 15-member macrolides have immunomodulatory properties and that their use could be justified in many diseases where inflammation plays a fundamental role in pathogenesis. A real disadvantage, resulting from widespread use, would be increased resistance of common pathogens such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, or even environmental mycobacteria. Furthermore, there could be cross-resistance to other antibiotics. Although few well-designed studies are available, the clinical impact of administering macrolides to patients with diffuse panbronchiolitis seems clear. In other respiratory diseases, such as bronchiectasis,

bronchiolitis obliterans, asthma, and chronic bronchitis, a cautious approach should be adopted while we wait for well-designed trials showing evidence of clinical benefit. The most scientifically rigorous studies are those carried out in patients with cystic fibrosis, although, for the moment, unanswered questions—the relevance of age at onset, type of bacterial colonization, severity—prevent widespread use of this family of drugs. The profile of the patient who is a candidate might involve colonization by *P aeruginosa*, frequent exacerbations, and a gradual decline in lung function, with exclusion of infection by environmental mycobacteria. However, anti-inflammatory effects have been observed to disappear at approximately 1 month after discontinuation; therefore, administration should be continuous (daily regimen, 3 days per week, or perhaps once per week, if a dose as high as 1500 mg is administered). We also need more studies to establish the pattern of efficacy, safety, and tolerability in each clinical condition before these drugs can be used in the long term. The development of a new family of macrolides is currently being investigated. These drugs, known as immunolides, lack the antibiotic effect and function as immunomodulators. Perhaps the future lies with them.[48]

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