Anti-inflammatory effects of macrolides in childhood lung diseases*

Efeito anti-inflamatório dos macrolídeos em doenças pulmonares da infância

Fernanda Luisi, Thays Dorneles Gandolfi, Arthur Dondonis Daudt, João Pedro Zelmanowicz Sanvitto, Paulo Márcio Pitrez, Leonardo Araujo Pinto

Abstract

Macrolides are drugs that have antimicrobial effects, especially against intracellular pathogens. Various studies have shown that macrolides might also have anti-inflammatory effects. Macrolides inhibit the production of interleukins and can reduce pulmonary neutrophilic inflammation. Clinical trials have demonstrated beneficial effects of macrolides in various chronic lung diseases. The objective of this study was to review recent data in the medical literature on the anti-inflammatory effects of macrolides in childhood lung diseases by searching the Medline (PubMed) database. We used the following search terms: "macrolide and cystic fibrosis"; "macrolide and asthma"; "macrolide and bronchiolitis obliterans"; and "macrolide and acute bronchiolitis". We selected articles published in international scientific journals between 2001 and 2012. Clinical studies and in vitro evidence have confirmed the anti-inflammatory effect of macrolides in respiratory diseases. Some clinical trials have shown the benefits of the administration of macrolides in patients with cystic fibrosis, although the risk of bacterial resistance should be considered in the analysis of those benefits. Such benefits are controversial in other respiratory diseases, and the routine use of macrolides is not recommended. Further controlled clinical trials are required in order to assess the efficacy of macrolides as anti-inflammatory drugs, so that the benefits in the treatment of each specific clinical condition can be better established.

Keywords: Macrolides; Asthma; Cystic Fibrosis; Bronchiolitis.

Resumo

Os macrolídeos são fármacos com efeitos antimicrobianos especialmente contra patógenos intracelulares. Vários estudos têm demonstrado possíveis efeitos anti-inflamatórios dos macrolídeos. Esses medicamentos inibem a produção de algumas interleucinas e podem reduzir a inflamação neutrofílica pulmonar. Ensaios clínicos têm demonstrado efeitos benéficos dos macrolídeos em diversas doenças pulmonares crônicas. O objetivo deste estudo foi revisar os dados recentes da literatura médica sobre os efeitos anti-inflamatórios dos macrolídeos nas doenças respiratórias da infância, através da pesquisa da base de dados Medline (PubMed) dos seguintes termos em inglês: "*macrolide and cystic fibrosis*"; "*macrolide and asthma*"; "*macrolide and bronchiolitis obliterans*"; e "*macrolide and acute bronchiolitis*" Foram selecionados artigos publicados em revistas científicas internacionais entre 2001 e 2012. Estudos clínicos e evidências in vitro comprovam o efeito anti-inflamatório dos macrolídeos em doenças respiratórias. Alguns ensaios clínicos demonstram benefícios na administração de macrolídeos em pacientes com fibrose cística; porém, o risco de resistência bacteriana deve ser considerado na análise desses benefícios. Tais benefícios são controversos em outras doenças respiratórias, e seu uso rotineiro não está indicado. Mais estudos clínicos controlados são necessários para avaliar a eficácia desses medicamentos como anti-inflamatórios. Dessa forma, poderemos definir melhor os benefícios dos macrolídeos no tratamento de cada uma das situações clínicas especificadas.

Descritores: Macrolídeos; Asma; Fibrose Cística; Bronquiolite.

* Study carried out at the Infant Center, Biomedical Research Institute, *Pontifícia Universidade Católica do Rio Grande do Sul* – PUCRS, Pontifical Catholic University of Rio Grande do Sul – Porto Alegre, Brazil.
Correspondence to: Leonardo A. Pinto. Avenida Ipiranga, 6690, 2º andar, Instituto de Pesquisas Biomédicas, CEP 90610-000, Porto Alegre, RS, Brasil.
Tel. 55 51 651-1919. E-mail: leonardo.pinto@pucrs.br
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Introduction

Macrolides are a group of drugs that are widely used in the treatment of various infectious diseases. These drugs act by inhibiting protein synthesis and bacterial growth, precluding the synthesis of vital proteins and causing the death of the pathogen. Some studies have reported that, in addition to their antimicrobial activity, macrolides have anti-inflammatory and anti-viral properties.[1,2] More recent studies have assessed this class of medications as immunomodulatory drugs in several respiratory diseases, although the recommendation of their use in these conditions remains relatively controversial.[1,3,4] The anti-inflammatory mechanism of macrolides was originally discovered in Japan in the 1980s, when treatment with macrolides significantly increased survival in patients with diffuse panbronchiolitis (DPB), a severe chronic lung disease with intense neutrophilic inflammation.[5]

Among the most important effects of macrolides are the inhibition of pro-inflammatory cytokine synthesis and secretion and the increase in anti-inflammatory cytokine secretion, as well as effects on neutrophil activity via inhibition of neutrophil migration to sites of inflammation.[6,7] Macrolides can also inhibit leukocyte degranulation, reduce eosinophilic inflammation, activate macrophage phagocytic activity,[7] and increase mucociliary transport, reducing mucus production in vivo[8,9] and in vitro.[6] In addition, these drugs can have an effect on adaptive immunity via regulation of T-cells and of antigen presentation. Studies have demonstrated a reduction in the number of lymphocytes in bronchoalveolar lavage samples, increased apoptosis of activated lymphocytes, and suppression of pro-inflammatory cytokine production by T-cells.[7] Other reported effects include reduced goblet cell secretion, reduced bronchoconstriction induced by a decreased release of endothelin-1, and inhibition of the cholinergic response in the airway smooth muscle.[2,8] A summary of the anti-inflammatory mechanisms is provided in Chart 1.

In a number of childhood lung diseases (acute bronchiolitis, cystic fibrosis, asthma, etc.), neutrophils play either a central or a supporting role in the onset and maintenance of inflammation, and recent studies have investigated the anti-inflammatory effects of macrolides in such diseases.[10,11] In the present article, we describe the anti-inflammatory effects of macrolides, as well as evaluating and discussing the indications for their use in various childhood respiratory diseases, on the basis of the most current data in the medical literature.

Methods

We chose four respiratory diseases that are relevant to pediatric practice and on which there are sufficient data to justify this review. We searched the Medline/PubMed database by using the following search strings: "macrolide" AND "cystic fibrosis"; "macrolide" AND "asthma"; "macrolide" AND "bronchiolitis obliterans"; and "macrolide" AND "acute bronchiolitis". All searches were conducted between December of 2011 and August of 2012, and we limited our searches to articles published in 2001 or later. We performed additional searches in which we replaced the term "macrolide" with the three major representatives of the macrolide class: "erythromycin", "azithromycin", and "clarithromycin". We used the following filters: clinical studies in humans; meta-analyses; guidelines; and published in English. We also included some experimental studies in order to flesh out the discussion of the anti-inflammatory mechanisms of this class of medications.

Chart 1 - Major immunomodulatory effects of macrolides.

Inhibition of cytokines or inhibition of inflammatory pathways	Reference
↓ activation of transcription factors in the bronchial epithelium	Desaki et al.[54]
↓ TNF-α secretion in bronchial epithelial cells	Cigana et al.[55]
↓ TNF- α, IL-1, IL-4, and IL-8 expression in various cells	Reato et al.[56]
Inhibition of innate immunity components	
↓ phagocytic capacity of polymorphonuclear cells	Theron et al.[57]
↑ apoptosis of neutrophils, lymphocytes, and eosinophils	Kadota et al.[58]
↓ neutrophil chemotaxis	Tsai et al.[59]
↓ mucus secretion in the airways	Shimizu et al.[60]

Results

The criteria described above were applied to all searches. Using the search string "macrolide" AND "cystic fibrosis", we identified 34 articles, of which 26, 25, and 6 were related to erythromycin, azithromycin, and clarithromycin, respectively. Using the search string "macrolide" AND "asthma", we identified 25 articles, of which 16, 9, and 7 were related to erythromycin, azithromycin, and clarithromycin, respectively. Using the search string "macrolide" AND "bronchiolitis obliterans", we identified 24 articles, 8 of which were related to erythromycin, 8 of which were related to azithromycin, and none of which were related to clarithromycin. Using the search string "macrolide" AND "acute bronchiolitis", we identified 14 articles, of which 3, 3, and 1 were related to erythromycin, azithromycin, and clarithromycin, respectively. These articles were reviewed again in order to exclude overlapping studies and those that were irrelevant for the theme of the review (evidence on the anti-inflammatory activity of these drugs). The remaining articles are listed in the references section of the present study and are discussed separately, considering in vitro/in vivo evidence of anti-inflammatory efficacy or clinical efficacy in each of the diseases studied. When only clinical trials of cystic fibrosis were looked at, we identified 4 involving only children, 5 involving children and adults, and 1 involving only adults. We identified 4 clinical trials of bronchiolitis obliterans all involved adults. For asthma, we identified 1 clinical trial involving children and 1 involving adults. For acute bronchiolitis, we identified 3 clinical trials, all involving infants less than 1 year of age.

Discussion

Cystic fibrosis

Cystic fibrosis is a systemic autosomal recessive hereditary disease that causes significant pulmonary impairment. A defect in the cystic fibrosis transmembrane conductance regulator gene results in abnormal epithelial ion transport, which causes increased mucus viscosity and consequent stasis of secretion in the lungs, contributing to an increased propensity for recurrent respiratory infections, especially with *Staphylococcus aureus*, *Haemophilus influenza*, and *Pseudomonas aeruginosa*. The infection and the inflammation lead to lung tissue damage, bronchiectasis, and progressive respiratory failure. Cystic fibrosis is similar to DPB in many ways.[12] Both are characterized by chronic sinusitis, neutrophilic airway inflammation, susceptibility to chronic bronchial infection with specific pathogens, and progressive deterioration of pulmonary function. The improvement in outcome for DPB patients treated with macrolides and the recognition that these drugs have various anti-inflammatory and immunomodulatory effects resulted in the hypothesis that the use of this class of antibiotics would be beneficial in the treatment of cystic fibrosis.[9,13] Macrolides have been shown to have positive effects on pulmonary function in cystic fibrosis, in addition to reducing secretion viscosity and airway adhesion of *P. aeruginosa*. They have also been shown to reduce the frequency of pulmonary exacerbations and to stabilize or improve respiratory capacity.[14]

In a randomized double-blind, placebo-controlled crossover trial,[15] the effects of azithromycin were evaluated in 41 children with cystic fibrosis over a 15-month period. Patients received either azithromycin or placebo for 6 months. Subsequently, there was a 2-month washout period, after which the treatments were crossed over. The primary outcome measure was change in FEV_1, and drug dose was adjusted for body weight (body weight ≤ 40 kg: 250 mg/day; body weight > 40 kg: 500 mg/day). Pulmonary function improved in both groups when patients were on azithromycin. In comparison with controls, patients given azithromycin had an improvement in FEV_1 of 5.4% (95% CI: 0.8-10.5), an improvement in FVC of 3.9% (95% CI: 2.5-9.2), and an improvement in $FEF_{25-75\%}$ of 11.4% (95% CI: 1.19-23.7%). Patients required fewer courses of other antibiotics when on azithromycin. No significant differences were found in sputum bacterial densities, exercise tolerance, or quality-of-life. The therapy was well tolerated, with no evidence of significant adverse events.[15]

Another study evaluated 60 clinically stable cystic fibrosis patients who received either azithromycin or placebo (250 mg/day) for 3 months. Pulmonary function levels were maintained in patients receiving azithromycin, whereas, in patients receiving placebo, there was a decline in FEV_1 and FVC of 3.62% and 5.73%, respectively. In addition, patients receiving

azithromycin had significantly fewer total days of i.v. antibiotic treatment, fewer days at home receiving i.v. antibiotics (p = 0.04), and fewer courses of i.v. antibiotics (p = 0.02).[16]

A major concern regarding the chronic use of macrolides in cystic fibrosis is related to the emergence of bacterial resistance to this class of antibiotics. One study evaluated the frequency of resistance to macrolides in *S. aureus* and *H. influenzae* isolates from cystic fibrosis patients, cultured between 1999 and 2004, a period in which there was a significant increase in the use of azithromycin in cystic fibrosis patients. Erythromycin resistance in isolated *S. aureus* strains increased from 6.9% to 53.8% in the period, and clarithromycin resistance in *H. influenzae* strains increased from 3.7% to 37.5%. Cultures from patients who received azithromycin yielded fewer positive results for both agents than did cultures from patients who did not receive azithromycin.[17]

Many unanswered questions can be raised as to how azithromycin should be used, including dose, dose interval, duration of effect, and impact of long-term treatment on disease progression and on the microbiological environment of the lung. In one clinical trial, children were randomized to receive either one of two doses of azithromycin (5 or 15 mg/kg/day) for 6 months in order to compare the effects of these doses. No differences in FEV_1, clinical scores, Pseudomonas colonization rates, pulmonary exacerbations, or need for antibiotics were found between the groups. The significant increase in the number of exacerbations and the decline in FEV_1 after azithromycin was discontinued in both groups suggest that the anti-inflammatory effect is a function of duration of use.[18] Another study analyzed azithromycin administered daily (250 mg/day) vs. azithromycin administered weekly (1,200 mg/week). The two groups showed equivalent improvement in pulmonary function. The once-weekly high dose regimen was associated with a moderate increase in gastrointestinal adverse effects.[19]

A recent systematic review analyzed clinical status and adverse effects in cystic fibrosis patients treated with macrolides vs. placebo.[20] Ten studies were included (959 patients). Eight of those studies compared azithromycin with placebo, and 2 studies compared the administration of different doses of azithromycin. Four clinical trials (549 patients) demonstrated that there were significant improvements in pulmonary function after treatment with azithromycin, when compared with placebo, at 6 months, the mean difference at 6 months being 3.97% (95% CI: 1.74-6.19). Data beyond six months were less clear, although reduction in the number of respiratory exacerbations was sustained. Patients treated with azithromycin were approximately twice as likely to be free of pulmonary exacerbations (OR = 1.96; 95% CI: 1.15-3.33), had a reduced need for oral antibiotics, and experienced a greater weight gain. In addition, treatment with azithromycin was associated with reduced identification of *S. aureus* in airway sample cultures. Adverse effects were uncommon and were not associated with azithromycin, although an increase in macrolide resistance was observed. Six studies were assessed as having a low potential for bias, whereas four had potentially significant risks for bias, although they had no major impact on the conclusion of the results or outcomes. The authors concluded that azithromycin has a small but consistent beneficial effect on the treatment of cystic fibrosis, the safety of use being satisfactory over a 6-month period, with a thrice-weekly dose regimen. However, considering the few long-term data available and the concern over the emergence of bacterial macrolide resistance, the evidence that is currently available is not strong enough to support the recommendation that all CF patients should receive azithromycin.[20]

The long-term effects of azithromycin were assessed in a follow-on study[21] involving cystic fibrosis patients who had participated in a randomized placebo-controlled clinical trial. Although at 6 months azithromycin did not acutely improve pulmonary function, it reduced the number of pulmonary exacerbations, decreased the initiation of new oral antibiotics, and increased the rate of weight gain. At 12 months, durability of response to azithromycin was observed, as measured by pulmonary exacerbations and weight gain.

Clarithromycin has been studied to a lesser degree as long-term treatment in cystic fibrosis patients. In a small pilot study conducted in the United States, 10 cystic fibrosis patients (19-26 years of age) infected with *P. aeruginosa* were treated with placebo for 3 weeks, followed by clarithromycin (500 mg, twice a day); there were no significant differences in neutrophil counts, nor in IL-8, elastase, or myeloperoxidase levels in sputum. According to the authors, these

findings might be due to the small number of patients or to the short duration of treatment.[22] However, one study involving 27 children showed a significant reduction in TNF-α, IL-8, IL-4, and IFN-γ levels in sputum and plasma, as well as an increase in the IFN- γ/IL-4 ratio and in peripheral lymphocyte response to phytohemagglutinin, after treatment with clarithromycin (250 mg/day) for 12 months.[23]

In contrast, an in vitro study demonstrated that azithromycin decreased IL-8 secretion only in non-cystic fibrosis cells and had no anti-inflammatory effects on cystic fibrosis epithelial or glandular cells.[24] A more recent double-blind study of clarithromycin vs. placebo found that, relative to placebo, treatment with slow-release clarithromycin for 5 months was not associated with significantly improved pulmonary function, weight gain, frequency of pulmonary exacerbations, or quality of life.[25]

Macrolides have been shown to slow the decline in pulmonary function in cystic fibrosis. The potential mechanisms of action include direct effects on the pathogen and on the host. A decrease in bacterial virulence, especially in *P. aeruginosa* virulence, and a late bactericidal effect, as well as a decrease in airway adherence of, motility of, and biofilm production by Pseudomonas, are the potential effects on the agent. The immunomodulatory effects on the host include suppression of the enhanced immune response and of the inflammation, inhibition of inflammatory cytokine production by alveolar macrophages, and decreased mucus hypersecretion.[11,23,26,27]

Various studies have shown positive results regarding the reduction in the number of exacerbations and regarding stabilization of or increase in respiratory capacity, whereas others have failed to demonstrate these effects (Chart 2). Treatment with azithromycin can have beneficial effects in cystic fibrosis, although the optimal dosage and duration of administration have yet to be well defined.[28] Two studies seem to synthesize the recommendations of and the controversies over the use of azithromycin in cystic fibrosis: while one study demonstrated significant benefits of treatment with azithromycin in children colonized with *P. aeruginosa*, another study undertaken by the same group of authors found no benefits of treatment with azithromycin in patients uninfected with *P. aeruginosa*.[29,30] In addition, it is essential to bear in mind the possibility that resistance to macrolides and other antibiotics will increase, as well as the clinical impact of colonization with more resistant pathogens.[18-20]

Bronchiolitis obliterans

Bronchiolitis obliterans is an inflammatory disease that affects the end of the airways, leading to obliteration of the bronchiole lumen. Bronchiolitis obliterans is the leading cause of death in the postoperative period after lung transplantation. It is one of the most common complications of allogeneic bone marrow transplantation (BMT) and, although its pathogenesis is still not completely understood, it is believed to be part of the graft-versus-host reaction. In contrast, bronchiolitis obliterans can occur in pediatric non-transplanted patients, following an infectious process.[27,31] The clinical manifestations characteristic of bronchiolitis obliterans include tachypnea, increase in the anteroposterior diameter of the chest, crackles, wheezing, and hypoxemia for at least 30 days after exposure to the triggering factor. The most common infectious agent responsible for the initial insult in post-infectious bronchiolitis obliterans is adenovirus, which occurs primarily in children.[32]

Approximately 10% of patients with graft-versus-host disease develop bronchiolitis obliterans, and prognosis is very poor (3-year mortality of 65%). Macrolides have been shown to decrease the progression of post-BMT bronchiolitis obliterans.[31] One group of authors[33] conducted an observational study involving 8 patients who underwent BMT and developed bronchiolitis obliterans. Treatment with azithromycin had positive effects, such as a 21% improvement in FVC and a 20% improvement in FEV_1. Another case study[34] also reported positive effects, although a randomized clinical trial found no differences in the results between the placebo and azithromycin groups.[35]

Post-lung transplant bronchiolitis obliterans is the most common form of the disease in developed countries and in adults, because of the larger number of procedures. Its pathogenesis and clinical findings are very similar to those of post-BMT bronchiolitis obliterans. The use of macrolides apparently prevents progression to bronchiolitis obliterans after lung transplantation, showing positive effects in the neutrophilic type

Chart 2 - Major studies contributing to the evaluation of the anti-inflammatory effects of macrolides in cystic fibrosis patients.

Authors	Design	Principal findings
Saint-Criq et al.[24]	Experimental	Azithromycin had no anti-inflammatory effect on epithelial or glandular cells of CF patients in vitro.
Zarogoulidis et al.[27]	SR	Macrolides reduce airway hyperresponsiveness and improve pulmonary function.
Southern et al.[20]	SR	The evidence that is currently available is not strong enough to support the recommendation that all CF patients should receive azithromycin, considering the concern over the emergence of bacterial resistance.
Saiman et al.[30]	RCT	Patients without chronic infection with PA showed no significant clinical benefit from treatment with azithromycin.
Kabra et al.[18]	RCT	No differences in FEV_1, pulmonary exacerbations, or need for antibiotics were found between the groups.
McArdle et al.[26]	Review	Long-term administration of macrolides leads to clinical benefits in CF patients.
McCormack et al.[19]	RCT	Equivalence was demonstrated between the two groups (daily vs. weekly use) with respect to improvements in pulmonary function.
Phaff et al.[17]	RCT	Erythromycin resistance in *S. aureus* isolates increased, as did clarithromycin resistance in *H. influenzae* isolates. Cultures from patients who received azithromycin yielded fewer positive results for both agents.
Rubin et al.[28]	Review	In vitro and in vivo studies suggest that macrolides inhibit the pulmonary influx of neutrophils, inhibit the release of cytokines, and improve the transportability of secretions
Pukhalsky et al.[23]	RCT	Treatment with clarithromycin significantly reduced TNF-α, IL-8, IL-4, and IFN-γ levels in sputum and plasma.
Saiman et al.[29]	RCT	Patients with chronic infection with PA showed significant benefit from treatment with azithromycin.
Equi et al.[15]	RCT	There was a significant improvement in pulmonary function associated with the use of azithromycin.
Wolter et al.[16]	RCT	Pulmonary function levels were maintained in patients receiving azithromycin, whereas, in patients receiving placebo, there was a decline in FEV_1 and FVC.

SR: systematic review; RCT: randomized clinical trial; CF: cystic fibrosis; and PA: *Pseudomonas aeruginosa*.

of the disease but not in the fibroproliferative type.[14,31]

The efficacy of treating bronchiolitis obliterans with macrolides in transplant recipients has been tested in adults, outcome measures varying across studies. Two studies that used similar but not identical measures reported conflicting results.[36,37] One study, involving 146 lung transplant recipients with a survival of more than 180 days (102 of whom were treated with clarithromycin and 44 of whom received standard postoperative care), demonstrated that clarithromycin did not reduce the incidence of bronchiolitis obliterans (76 patients treated with clarithromycin developed bronchiolitis obliterans, whereas 7 receiving standard care developed the disease) or the incidence of respiratory complications (35 patients treated with clarithromycin vs. 18 receiving standard care).[36] One study,[37] assessing forced expiratory volume in 11 patients over 10 months of unblinded treatment with azithromycin (250 mg, 3 times a week), demonstrated that there was no improvement in pulmonary function. Those authors, however, reported that there was a change in the natural history of bronchiolitis obliterans, since the disease did not progress during the assessment period.[37] This result is in contrast with the findings of another group of authors,[36] whose patients developed bronchiolitis obliterans regardless of treatment with a macrolide (clarithromycin), there being no change in the natural history of the disease. Therefore, the role of the use of macrolides in patients with post-transplant bronchiolitis obliterans has yet to be well defined.

The major risk factors for post-infectious bronchiolitis obliterans in children are adenovirus infection and the use of mechanical ventilation; many cases have been reported in South America.[32] This disease has a major clinical impact, as demonstrated in a study conducted in a hospital in Buenos Aires, Argentina, in which bronchiolitis obliterans was found to account for 14% of all hospital days in a 10-year period.[38] There have been no studies testing the efficacy of treatment with macrolides in patients with post-infectious bronchiolitis obliterans, and the determination of this efficacy is essential, given the major impact of this disease in developing countries.[39]

Asthma

Asthma is a chronic inflammatory disease whose main characteristics are bronchial hyperresponsiveness and chronic lower airway inflammation. These characteristics are responsible for variable airflow limitation, causing episodes of wheezing, dyspnea, chest tightness, and cough, which are often associated with respiratory infections during exacerbations. Worldwide, asthma results in high hospitalization rates and significant impairment of patient quality of life. Bronchial inflammation is the main pathophysiological characteristic of asthma and can be present even in asymptomatic patients. In addition to the inflammatory process, causing mucosal edema and mucus production, there is bronchospasm, further contributing to the decrease in airway caliber.[1]

Macrolides are known not only for their bacteriostatic effect but also for having an anti-inflammatory effect (reducing neutrophil counts).[5] Although the pathogenesis of asthma is complex, the importance of inflammatory cells and pro-inflammatory cytokine secretion is recognized, the major cells being Th2, eosinophils, and mast cells.[40] The positive effect of macrolides is controversial in various studies of asthma patients. However, the reduction in neutrophilic airway inflammation, in edema, and in bronchial hyperresponsiveness, as well as the inhibition of mucus production and the improvement in pulmonary function in asthma patients, are benefits associated with the potential immunomodulatory capacity of macrolides.[1,27,40]

Asthma exacerbations are related to allergens and infections, and rhinovirus seems to be one of the most common triggers of viral exacerbations. Although it has not been demonstrated that asthma patients experience viral infections more often than do healthy subjects, their symptoms seem to be more persistent and severe. A defect in IFN production seems to be related to the difficulty in eliminating the virus via apoptosis.[7,14] According to one study,[41] the airway epithelium of asthma patients produces more inflammation mediators than does the normal epithelium when infected with a virus.

It is certain that 40-80% of asthma exacerbations are triggered by viral infections, which induce a response, with an influx of neutrophils, eosinophils, mast cells, CD4 cells, and CD8 cells into the airways, together with the production of pro-inflammatory cytokines.[7,14,42] Similarly to viruses, atypical bacteria can cause bronchial inflammation, also leading to asthma exacerbations, as well as causing chronic airway infection and hindering disease control efforts.[7,43] With regard to bacterial infections, one study showed that when organisms such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* are responsible for asthma exacerbation, the use of macrolides improves disease control.[43]

A recent review[7] concluded that the routine use of macrolides in patients with uncontrolled asthma did not reduce symptoms or improve pulmonary function. However, a specific phenotype of asthma, determined by PCR testing of bronchoscopy samples for the presence and diversity of pathogens, can benefit from the use of macrolides.

The beneficial effects of macrolides have also been tested in the treatment of asthma that is not associated with infectious exacerbations. Clarithromycin and azithromycin have been shown to be efficient in reducing airway inflammation, the former having been associated with decreased airway edema and decreased TNF-α, IL-1, and IL-10 concentrations in nasal aspirates.[8,44,45] One group of authors demonstrated that azithromycin decreased IL-5 production in lymphocytes of children with atopic asthma, without affecting IFN- γ production, thereby showing that azithromycin has a beneficial effect on the pathogenesis of asthma.[40]

Even with all of these theoretical justifications based on experimental or mechanistic studies,[46] the positive effects of macrolides has not been consistent in the published clinical trials in

Chart 3 - Major studies contributing to the evaluation of the anti-inflammatory effects of macrolides in asthma patients.

Authors	Design	Principal findings
Good et al.[7]	Review	The documentation of the presence and diversity of infection in bronchoalveolar lavage samples can identify an asthma phenotype that responds favorably to therapy with macrolides.
Gao et al.[46]	Experimental	Macrolides were effective in improving chemotaxis, reducing the injury caused by airway inflammation.
Simpson et al.[44]	RCT	Clarithromycin was found to reduce airway inflammation, particularly neutrophilic inflammation.
Kraft et al.[43]	RCT	Asthma patients colonized with *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* who were treated with clarithromycin showed improvement in FEV_1 when compared with patients in the placebo group.

RCT: Randomized clinical trial.

asthma (Chart 3). Further studies investigating the effects of macrolides in asthma management are required. This research should focus not only on confirming that the use of macrolides has an anti-inflammatory effect in asthma but also on the impact of the benefits that these medications can bring to clinical practice.

Acute bronchiolitis

Acute bronchiolitis is the leading cause of hospitalization in infants. It is characterized by extensive lower airway inflammation, accompanied by increased mucus production and epithelial cell necrosis.[47] A clinical diagnosis of acute bronchiolitis is characterized by tachypnea, wheezing, and upper airway infection. The primary cause of acute bronchiolitis is infection with respiratory virus, especially respiratory syncytial virus, with widespread neutrophilic airway inflammation.[10,48] Antibiotics are not routinely recommended in the management of acute bronchiolitis, but some researchers have proposed the use of macrolides in the treatment of this disease.[47]

In one study,[49] 21 hospitalized children with moderate acute bronchiolitis received oral clarithromycin for 3 weeks and showed a significant reduction in duration of oxygen therapy, length of hospital stay, and 6-month post-discharge hospital readmission, which indicates a beneficial effect on disease severity. In contrast, in another study,[50] 71 children received azithromycin for 3 days and no significant result was found. Although the findings of those two studies are conflicting, a review[51] points out serious biases in them, such as the blinding, the randomization, the power of the sample, and even the data analysis. Therefore, the effects of the use of macrolides in acute bronchiolitis remain unclear, and clinical trials involving an adequate number of participants are therefore warranted.

Our group has recently demonstrated, in a large sample of hospitalized infants with acute bronchiolitis, that the use of azithromycin did not affect clinical outcomes, even when we stratified the analysis by viral identification. These findings suggest that azithromycin should not be used in infants presenting with their first episode of wheezing, and they could contribute to reducing the use of antibiotics in infants with acute bronchiolitis.[52]

Final considerations

One group of authors[53] demonstrated that the anti-inflammatory and antimicrobial activities of macrolides are independent and can be separated, which would make it possible to create new anti-inflammatory agents, particularly bearing in mind the potential risk of increasing bacterial resistance with the indiscriminate use of macrolides worldwide. Many studies have confirmed the anti-inflammatory effects of macrolides in respiratory diseases. Some clinical trials have demonstrated the benefits of the administration of macrolides in patients with cystic fibrosis. In other respiratory diseases, such benefits remain controversial, and the routine use of macrolides is not recommended. In the management of respiratory diseases, physicians should evaluate the prescribed treatments carefully and individually, as well as analyzing their capacity to reduce symptoms, length of hospital stays, and sequelae. In addition, obviously, physicians should monitor abuse of antimicrobial agents and devise new

strategies to change current medical practice. Finally, additional randomized controlled clinical trials involving a large number of patients are needed in order to assess the effects of macrolides in each clinical condition, so that the benefits of these drugs in the treatment of respiratory diseases can be established.

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About the authors

Fernanda Luisi
Physical Therapist specializing in Child Health, *Pontifícia Universidade Católica do Rio Grande do Sul* – PUCRS, Pontifical Catholic University of Rio Grande do Sul – Porto Alegre, Brazil.

Thays Dorneles Gandolfi
Student. *Pontifícia Universidade Católica do Rio Grande do Sul* – PUCRS, Pontifical Catholic University of Rio Grande do Sul – School of Medicine, Porto Alegre, Brazil.

Arthur Dondonis Daudt
Student. *Pontifícia Universidade Católica do Rio Grande do Sul* – PUCRS, Pontifical Catholic University of Rio Grande do Sul – School of Medicine, Porto Alegre, Brazil.

João Pedro Zelmanowicz Sanvitto
Student. *Pontifícia Universidade Católica do Rio Grande do Sul* – PUCRS, Pontifical Catholic University of Rio Grande do Sul – School of Medicine, Porto Alegre, Brazil.

Paulo Márcio Pitrez
Professor. *Pontifícia Universidade Católica do Rio Grande do Sul* – PUCRS, Pontifical Catholic University of Rio Grande do Sul – School of Medicine, Porto Alegre, Brazil.

Leonardo Araujo Pinto
Professor. *Pontifícia Universidade Católica do Rio Grande do Sul* – PUCRS, Pontifical Catholic University of Rio Grande do Sul – School of Medicine, Porto Alegre, Brazil.