Arch Bronconeumol. 2010;**46(5)**:244-254

ARCHIVOS DE BRONCONEUMOLOGIA

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Review Article

Usefulness of Macrolides as Anti-inflammatories in Respiratory Diseases

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ARTICLE INFO

Article history:
Received September 9, 2009
Accepted October 10, 2009

Keywords:
Macrolides
Antibiotic
Anti-inflammatory
Respiratory disease
Microbial resistance

ABSTRACT

The macrolides are antibiotics that, besides their anti-bacterial action, have an anti-inflammatory effect, by decreasing the activity of the immune cells and bacteria cell changes.

An increase the survival of patients suffering from diffuse panbronchiolitis was already seen in the 1980s, after being treated with erythromycin. Currently, the use of macrolides in various chronic inflammatory diseases has increased significantly. Clinical improvements associated to the administration of macrolides have been observed in diseases such as, cystic fibrosis, asthma, and bronchiectasis.

However, despite the apparent clinical benefit they seem to provide, the published results up until now are controversial and conclusive results are unable to be obtained. This means that further clinical trials are necessary to confirm or refute the long-term use of these drugs, which are not free of adverse effects, mainly the appearance of resistant bacteria.

Utilidad de los macrólidos como antiinflamatorios en las enfermedades respiratorias

Palabras clave:
Macrólidos
Antibiótico
Antiinflamatorio
Enfermedad respiratoria
Resistencias microbianas

RESUMEN

Los macrólidos son antibióticos que además de su acción antibacteriana pueden presentar un cierto efecto antiinflamatorio por disminución de la actividad de las células inmunitarias y alteración de las células bacterianas.

Ya en los años 80 se observó un aumento de la supervivencia en pacientes afectados de panbronquiolitis difusa después de tratarse con eritromicina. En la actualidad, el uso de macrólidos en diferentes enfermedades de carácter inflamatorio crónico ha aumentado significativamente. En la fibrosis quística, el asma, las bronquiectasias, entre otras, se han observado mejoras clínicas asociadas a la administración de macrólidos.

Sin embargo, y a pesar del aparente beneficio clínico que parecen aportar, los resultados publicados hasta la fecha son controvertidos y no permiten obtener resultados concluyentes. Esto hace necesario realizar futuros ensayos clínicos para confirmar o rebatir el uso a largo plazo de estos fármacos, que no están exentos de efectos adversos, principalmente la aparición de especies bacterianas resistentes.

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0300-2896/$ - see front matter

Introduction

Macrolides are antibiotics that are characterized by having a macrocyclic lactone ring composed by : i) 14 atoms: erythromycin, clarithromycin, oleandomycin, or roxithromycin; ii) 15 atoms: azythromycin, or iii) 16 atoms: spiramycin and josamycin. Each of these act by inhibiting the synthesis of proteins at the union with the bacterial 50s ribosomal subunit and block the process of translocation. They are principally bacteriostatic antibiotics, although depending on the species of bacteria, size of the inoculum, bacterial growth phase, and biophase concentrations of the antibiotic, can also have bactericidal effects. The first macrolide (erythromycin) has antibacterial activity against the majority of gram-positive cocci and some anaerobes and gram-positive bacilli. The gram-negative bacilli are inherently resistant to erythromycin.[1]

The integration of new macrolides into the market, such as clarithromycin and azythromycin, has given way for new therapeutic options for the treatment of bacterial infections that, in general, are resistant to other antibiotics.[2] The pharmacokinetic characteristics of the macrolides, such as their elevated volume of distribution and intracellular accumulation, allow for high tissue concentrations, which in the respiratory tract can reach 50 to 100 times greater than in plasma concentrations.[3,4] Clarithromycin also has activity against *Chlamydia* sp., *Legionella* sp., *Mycoplasma* sp., *Mycobacterium avium complex* and *Helicobacter pylori*. Unlike erythromycin, azythromycin has activity against the majority of gram-negative bacteria, including aerobes such as *Haemophilus* sp., *Moraxella* sp. o *Neisseria* sp.

Furthermore, macrolides have anti-inflammatory and immunomodulating activity, as shown in both *in vivo* and *in vitro* studies, using both animal and human models in different clinical situations.[5,6] These other properties confer a different role on the macrolides that divers from their classical uses as antibiotics and introduce new therapeutic possibilities.

Mechanisms of Action

The exact mechanisms of action for the macrolides that have this anti-inflammatory action are still not completely defined, although it is known that they act by various molecular, cellular, and bacterial mechanisms (table 1).

The effects of macrolides on host cells include alterations in rheological properties and mucous production. A randomized clinical trial on 31 patients with double blind and placebo controls administered clarithromycin at a dosage of 100mg 2 times per day for 8 weeks.[7] The patients initially presented with mucus hypersecretion associated with chronic bronchitis, bronchiectasis, or diffuse panbronchiolitis, and in over 50% of cases, not only was a decrease in production and secretion of mucus observed, but also an increase in ciliary clearance along with greater ease of expectoration. Other studies reported similar results from using clarithromycin at a dosage of 400 mg/day for 7 days, with an increase in sputum production in 38% of patients.[8] These same effects had previously been described for erythromycin.[9.]

Furthermore, macrolides interfere with the function of neutrophils and macrophages in the respiratory tract, disrupting the processes of chemotaxis, migration, and cellular activity.[10,11] These disruptions affect cell survival, since azithromycin, clarithromycin, and roxithromycin induce apoptosis of lymphocytes and neutrophils.[12-16] The function of molecules involved in the processes of adherence is also disrupted since erythromycin, roxithromycin, and clarithromycin are capable of diminishing their expression.[17-20]The production of proinflammatory cytokines is also reduced following application of macrolides. Various interleukins (IL) that play an important role in inflammation, such as IL-1, IL-6, and IL-8, among others, are clearly inhibited in their expresion.[21-26] Other acute-phase inflammatory mediators that also show a reduced expression in the presence of macrolides are TNF-α and IFN-γ.[27-29] In contrast, the effect of macrolides on the expression of leukotrienes and cell growth factors appears to be irrelevant.[30,31] Furthermore, various oxidizing species that take part in the innate immunity of neutrophils, such as the superoxide anion and nitric oxide, are also diminished by the action of erythromycin, clarithromycin, and roxithromycin.[32-35]

These diminishing effects on mediators have their origin in the changes caused by the macrolides on the junction of several nuclear transcription factors, such as nuclear factor-kappa B (NF-κ-B) and activator protein-1 (AP-1), and the junction of promoters to the DNA of the implicated genes, and it is speculated that glutathione deficiency could activate these mechanisms.[36-40] Disturbances in intracellular signalling pathways, such as in protein kinases (mitogen-active protein kinases), could also inhibit expression of these genes.[41-44]

Table 1
Mechanisms of action implicated in the anti-inflammatory activity of macrolides

	Effects and characteristics
Mechanisms of action for macrolides in host cells	
Mucous production and rheological properties	Decreased secretion, increased elasticity and ciliary movement
Functionality in immune system cells	Decreased chemotaxis, migration, and cellular activity in neutrophils and macrophages. Increased apoptosis
	Decreased chemotaxis, migration, and cellular activity in neutrophils and macrophages. Increased apoptosis
	Decreased expression of cellular adherence molecules: Mac-1, ICAM-1, beta-2-integrins (CD11b/CD18), E-selectin, LFA-3 and VCAM-1
Cytokine production	Decrease in IL-1β, IL-6, IL-8, IL-4, IL-5, TNF-α, IFN-γ, $PGF_{1\alpha}$, PGE_2 and GM-CSF. No changes in IL-2 and LTB_4
Production of oxidizing species	Decrease in superoxide anion, NADPH oxidase, and nitroso-synthase
Nuclear transcription factors and gene regulation pathways	Changes in NF-Î-B and AP-1 DNA junctions and promoters for proinflammatory cytokine genes
	Inhibition of the expression of genes coding for mucoid proteins via ERK
Intracellular signalling metabolic pathways	*Altered protein kinase pathway (MAPK): JNK*
Membrane transporters	Increased expression of MPR1 and MDR1
Cell junctions	Increased expression of molecules for tight junctions, claudins, occludins, and JAM
Plasma antibodies	No effects in BPI-ANCA
Macrolide mechanisms of action in bacterial populations	
Effects on *Pseudomonas aeruginosa*	Altered virulence factors: decreased biofilm production and reduced mobility
	Altered quorum sensing system: reduced transcription of implicated genes (lasl and rhIR). Decreased expression of stress proteins (Gro-ELK)

DNA: deoxyribonucleic acid; AP-1: activator protein-1; BPI-ANCA: antineutrophil cytoplasmic autoantibodies against bactericidal permeability-increasing protein; CD: cluster of differentiation; ERK: extracellular signal regulated kinase; GM-CSF: granulocyte-macrophage colony stimulating factor; ICAM-1: intercellular adhesion molecule 1; IFN: interferon; IL: interleukin; JAM: junction adhesion molecules; JNK: c-jun N-terminal kinase; LFA-3: lymphocyte function-associated antigen 3; LTB_4: leukotriene B-4; Mac-1: macrophage adhesion molecule 1; MAPK: mitogen active protein kinase; MDR1: multidrug resistance protein 1; MPR1: multidrug resistance associated protein 1; NADPH: nicotinamide adenine dinucleotide phosphate reduced; NF-κ-B: nuclear factor-kappa B; PGE_2: prostaglandin E-2; PGF_{1a}: prostaglandin F-1a; TNF-a: tumour necrosis factor alpha; VCAM-1: vascular cell adhesion molecule 1.

Macrolides induce the expression of cellular transporters, as in the case of azithromycin administered (500 mg/day) for one month, which induces the expression of multidrug resistance-associated protein-1. This transporter belongs to the class of the adenosine triphosphate binding cassettes (ATP binding cassette), the same class that encompasses the chloride ion transporters known as cystic fibrosis transmembrane conductance regulators (CFTR), which become compromised in cystic fibrosis (CF). By treating the transporters that function with similar mechanisms of action, the expression of the multidrug resistance-associated protein-1 would imply a compensating mechanism for chloride ion transport, and thus might be able to replace the damaged CFTR transporters, which has an end result of a clear clinical benefit.[45-58]

Azithromycin also affects cell junctions. Hermetic or "tight" junctions are located in the membranes of epithelial cells and form part of the barrier that regulates the movement of ions and solutes between them. Azithromycin induces the formation of the proteins that form tight junctions, an effect that erythromycin appears not to have.[49]

Azithromycin has also been studied in its effects on antineutrophil cytoplasmic autoantibodies against bactericidal permeability-increasing protein (BPI-ANCA). BPI is a protein associated with neutrophil membranes that confers bactericidal and antiendotoxin properties. Elevated levels of anti-BPI antibodies are found in CF patients that cancel out these defensive effects, which is correlated with a deterioration of pulmonary function and greater colonization by *Pseudomonas aeruginosa.* The hypothesis that macrolides can diminish BPI-ANCA has been studied using a randomized clinical trial with double blind and placebo controls over three months. This study administered azithromycin (250 mg twice per week) to 18 CF patients, and no significant effect was detected in diminishing BPI-ANCA.[50]

The effects that macrolides have on bacterial populations and that allow explanation of their anti-inflammatory activity are the result of disturbances in virulence factors and communication mechanisms.[51,52] In the case of *P. aeruginosa*, one of the mechanisms that confers resistance to the natural defences of the host and reduced sensitivity to antibiotic activity is the formation of a protective external layer composed of alginates, also called a biofilm. Clarithromycin and azithromycin inhibit attachment and slow the growth of biofilms.[53,54] The formation of biofilms and virulence factors in *P. aeruginosa* are controlled by a communication system between the bacteria known as quorum sensing.[55,56] Macrolides inhibit several genes implicated in protein expression in these systems. For instance, azithromycin reduces the transcription of lasI and rhlR as well as some stress proteins, such as Gro-ELK, which causes decreased bacterial mobility, increased susceptibility to phagocytosis, and increased bacterial mortality.[57-59] Other mechanisms inherent to macrolides that are implicated in hindering the formation of biofilms include inhibition of guanosine-diphospho-D-mannose-dehydrogenase and fimbriae disruption.[60-62]

Anti-inflammatory Effects of Macrolides and their Use in Respiratory Diseases

Since the use of macrolides commenced in the 1970s for the treatment of asthma, and following results from use in patients with diffuse panbronchiolitis (DPB), its use as an anti-inflammatory treatment was extended to other respiratory diseases, such as CF, chronic obstructive pulmonary disease (COPD), bronchiectasis, and bronchiolitis obliterans syndrome (BOS), among others.[63,64]

Diffuse Panbrochiolitis

DPB is a chronic respiratory disease with an unknown aetiology, almost exclusively described in adult males from Japan, which has several similarities to CF[65]. This disease is characterized by a chronic inflammation of the respiratory tract along with progressive destruction of the pulmonary parenchyma. The microorganisms that initially colonize the respiratory tract in these patients are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus*. Subsequently, *P. aeruginosa* with a mucoid phenotype has been found in up to 70% of patients, which implies a 5-year survival rate of just 8%. By adding an oral administration of erythromycin to the conventional treatment, mortality diminishes substantially and survival increases to up to 92%.[64-67] Clarithromycin has also shown its usefulness in this disease, producing similar results to those described using erithromycin.[68]

Cystic Fibrosis

CF is characterized by a disruption or absence of the CFTR that regulates the flow of chloride ions through the surface of the epithelial cells. This causes gastrointestinal and respiratory secretions to become more viscous and thick, which obliterates these tracts, promoting infections and the appearance of lesions from inflammatory and toxic bacterial by-products. Pathogens that dominate the initial stages of this disease are *S. aureus* and *H. influenzae*. In more advanced phases, colonization is predominantly by *P. aeruginosa* of the mucoid type (biofilm producers). The immune system concentrates the presence of a high quantity of neutrophils in the respiratory tract that triggers a major inflammatory response with production of cytokines and oxidizing products that damage the pulmonary parenchyma.

The use of macrolides to treat CF is based on the results obtained in patients with DPB and the numerous similarities between the two diseases.[65] Table 2 summarizes the principal clinical studies testing macrolides in patients with CF.

Since Jaffe et al[69] published the first study providing a formal record of the contribution of a macrolide (azithromycin) to the treatment of CF, several new results have been published on the use of macrolides. Various observational studies on the use of azithromycin in CF[70-75] show improvement in pulmonary function as shown by the forced expired volume in first second (FEV_1) with increases between 1.07[73] and 21%.[70] These studies also show a general improvement in forced vital capacity (FVC) between 0.97 and 16.4%, although not always with statistical significance.[71] Only in one of the studies was the absence of colonization by *P. aeruginosa* not used as an exclusion criteria[72] and, although positive results do exist (improvement in pulmonary function and increase in patient's weight), the results of this study are globally presented without a subgroup analysis of uncolonized patients. These studies show other interesting results, such as: i) a general increase in patient's weight and body mass index; ii) disparity between microbiological controls, since although some studies did not show any changes in the typical flora,[71] others showed a significant decrease in mucoid morphotype *P. aeruginosa* in sputum samples,[73,75] decreases in *S. Aureus,* or increases in *Stenotrophomonas maltophilia,*[75] and iii) the effects of decreasing symptoms of exacerbation and the use of intravenous antibiotics varies between those that show a positive effect, fewer exacerbations, and fewer antibiotics,[74] and those that show no changes.[75] It should be noted that important secondary effects were noted in none of these studies.

Since Wolter et al[76] presented the results of their study, 5 randomized clinical trials with double blind and placebo controls that used azithromycin in CF patients have been published. The populations studied primarily corresponded to young patients, and only one study was performed in adults.[76] Colonization by *P. aeruginosa* was an inclusion criterion in only 2 of the studies,[78,82] while the rest of the studies made no note of this factor.[76,77,80] The macrolide dose used in these studies was similar: 250mg of azithromycin 3 times a week if the patient weighed less than 40 kg,

Table 2
Studies performed with macrolides in patients with cystic fibrosis

Reference	Study design	No. of patients; mean age (interval ± SD) in years	Drug; posology; mean duration (interval) in months	Results and comments
Jaffé et al, 1998[69]	Open, not randomized	7; 12.1 (5.8–16.8)	AZM; ND; 7.2 (3.6–14.4)	ΔFEV_1: 11% ΔFVC: 11.3%
Anstead et al, 1999[70]	Open, not randomized	20; ND	AZM; 250mg/48h; 9.4 (2–18)	ΔFEV_1: 21% No discernable adverse effects
Anstead et al, 2000[71]	Open, not randomized	14; 24 (12–36)	AZM; 250mg/48h; 22.3 (16–33)	ΔFEV_1:18.9%; ΔFVC: 10.4% No change in weight, colonization, or resistance
Pirzada et al, 1999[72]	Retrospective, cases and controls	36; ND	AZM; 250mg/day; 9.4	ΔFEV_1: 5.9%; ΔFVC: 9.4% (with respect to the control group) Increased weight gain
Ordoñez et al, 2001[83]	Prospective simple-blind	10; ND (19–26)	Clarithromycin; 500 mg/12h; 1.5	No changes in FEV_1, FVC or inflammation markers
Hansen et al, 2002[73]	Retrospective	50; 30.1 (18.1–53.8)	AZM; 250 mg/day; 8 (4–12)	ΔFEV_1: 1.07%; ΔFVC: 0.97%
Wolter et al, 2002[76]	Prospective randomize, double-blind with placebo controls	60; 27.9 (18–44)	AZM; 250mg/day; 3	ΔFEV_1: 3.6%, ΔFVC: 5.7% (with respect to the control group) In the AZM group: fewer ATB cycles i.v., fewer days of ATB i.v. and improved quality of life. Decreased CRP
Equi et al, 2002[77]	Prospective cross-group, randomized, double blind, with placebo controls	41; 13.8 (8.1–18.6)	AZM; 250mg/day (if ≤ 40 kg) and 500mg/day (if > 40 kg); 6	ΔFEV_1 (with respect to the control group): 5.4%. In the AZM group: fewer cycles of oral antibiotics; no changes in inflammation markers
Pirzada et al, 2003[74]	Retrospective, cases and controls	20; 18.6 (ND)	AZM; 250mg/day; 21	ΔFEV_1: 17.6% and ΔFVC: 16.4% (with respect to the control group). In the AZM group: fewer severe exacerbations and greater weight gain
Saiman et al, 2003[78]	Prospective randomized, double blind, with placebo controls	185; 20.4 (ND)	AZM; 250 mg/day, 3 days a week (if ≤ 40 kg) or 500 mg/day 3 days a week (if > 40 kg); 5.6	Colonization by *Pseudomonas aeruginosa* is an inclusion criteria ΔFEV_1: 6.2%; ΔFVC: 5% (with respect to placebo group) In the AZM group: fewer exacerbations, shorter hospitalization time, greater weight gain, and no changes in inflammation markers
Hansen et al, 2005[75]	Observational, prospective, cohort study	45; 29 (17.5–50)	AZM; 250mg/day; 12	Improved BMI and nutritional state; improved FEV_1 and FVC ↓ mucous *P. aeruginosa* strains; ↓ CRP; no changes in ATB treatment. Few adverse side effects
Clement et al, 2006[80]	Prospective randomized, double blind, with placebo controls	82; 11 (±3.3)	AZM; 250mg/day, 3 days a week (if ≤ 40 kg) or 500mg/day 3 days a week (if > 40 kg); 12	ΔFEV_1 no significant differences between the 2 groups ↓ no. of exacerbations in the AZM group and colonized subgroup ↓ no. of oral ATB in the AZM group and colonized subgroup No discernable adverse effects
Steinkamp et al, 2008[82]	Prospective randomized, double blind, with placebo controls	38; 23.7 (±7.6)	AZM; 20-29 kg: 500 mg, 30-39 kg: 750 mg, 40-49 kg: 1,000 mg, ≥50 kg, 1,250mg. Once/week; 8	Colonization by *Pseudomonas aeruginosa* is an inclusion criteria. ΔFEV_1: −3.7% ↓ in inflammation markers: CRP, IL-8 and LBP ↓ in *P. aeruginosa* cultures and alginate in sputum Improved quality of life. Few adverse side effects

ΔFEV_1: difference between final and initial forced respiratory volume in one second; ΔFVC: difference between final and initial forced vital capacity; ATB: antibiotic; AZM: azithromycin; SD: standard deviation; ACE inhibitor: interleukin; BMI: body mass index; ESWL: intravenous; LBP: lipopolysaccharide binding protein; ND: no data; CRP: C-reactive protein.

or 500mg if the patient weighed more than 40 kg, although in the study performed in adults only,[76] the dosage was not adjusted to the patient's weight and all patients received a fixed dose of 250 mg. As an exceptional case, the study by Steinkamp et al[82] is the only one that used a single weekly posology that was adjusted by weight: 20–29kg (500mg); 30–39kg (750mg); 40–49kg (1,000mg), and equal to or heavier than 50kg (1,250mg).

An improvement in pulmonary function was observed in 3 of the studies with increases in FEV_1 and in 2 of the studies with increases in FVC. In two other studies,[80,82] no significant differences were found in these two parameters when compared to placebo groups. Specifically, in one of these[82] an inverse tendency was observed where pulmonary function decreased with respect to baseline levels, although this might be justified by the fact that the study was started immediately after administering a course of antibiotics, which was not the case in the other studies.

The majority of trials concur that the use of azithromycin provides a reduction not only in the number of exacerbations, but also in the number of antibiotic treatment courses needed, which implies a reduction in the duration of hospitalization of approximately 3 to 5 days.[76,78] An improvement in the patient's quality of life was observed in 3 of the trials with various scales of measurement.[76,78,82]

Regarding the mechanisms of action, 2 of the studies documented a reduction in C reactive protein in the group treated with azithromycin,[76,82] while others found no differences in IL-8 production compared to placebo patients, although they did find differences in elastase production.[77,78] Two of the trials reported adverse effects, primarily in the gastrointestinal tract.[76,78] In this respect, it should be noted that the azithromycin given in the Steinkamp et al[82] study as a single weekly dose presented no more adverse effects than in other studies, as would have been expected.[81]

Regarding the effect of the treatment on bacterial flora, only the study by Saiman et al[78] showed that the long-term use of azithromycin produced the appearance of methycilin-sensitive *S. aureus* strains (in less than 10% of patients), while colonization by *P.aeruginosa* showed no changes. However, Steinkamp et al[82] showed a 25% reduction in

sputum cultures positive for *P. aeruginosa* after 8 weeks of azithromycin treatment as well as a slight reduction in cultures positive for *S. aureus*.

Given the heterogeneity observed in response to treatment, Saiman et al[78] decided to study the relationship between clinical response to the treatment and *in vitro* phenotype of *P. aeruginosa* in a subgroup made up of the 41 of the 81 patients that were included in the trial that showed the greatest variability in response to azithromycin (increases in FEV_1>10% or decreases <5%).[79] They observed that the phenotype that complied with the criteria for selection as "change in phospholipase C" correlated with the possible clinical results obtained, with a significant correlation with change in FEV_1 and number and duration of exacerbations, leading the authors to conclude that a prior identification of phospholipase C phenotypes would contribute to an improved clinical result when administering azithromycin to patients with CF given the correlation between this phenotype and patient improvement in the parameters for pulmonary function. In a similar manner, Clement et al[80] performed a stratification of the results, showing that the sub-population of patients with CF that lacked colonization by *P. aeruginosa* (first stages of the disease) is also a group that may benefit from clinical improvements under the application of azithromycin.

The differences in posology were studied in a double blinded clinical trial performed on 208 young patients (mean age: 21.2 years) with CF. These patients were randomized to receive azithromycin in a daily (250 mg) or a single weekly (1,200 mg) dose for 6 months. No differences were found between the two groups when comparing FEV_1 and FVC levels, the number of hospital admissions or days of hospitalization, quality of life, or the bacterial populations in cultures. Improvements in older patients were significant with respect to weight and height in the daily treatment group. The patients with a single weekly dose presented more secondary gastrointestinal effects than the other group, and 5 patients infected with *S. aureus* developed resistances to azithromycin during the treatment period.[81]

Only one study has evaluated the effects of clarithromycin on CF. Following 6 weeks of treatment, no significant improvements were seen in pulmonary function (FEV_1 and FVC) or in the different inflammation markers. Only one patient presented a clinically significant improvement in FEV_1, and had a better response to the immunoglobulin (Ig) dose for *Mycoplasma pneumoniae*, for which it appears that the improvement shown was not due to the anti-inflammatory effect (without changes in inflammation markers) in this case, but to the antibiotic effect of the macrolides.[83]

Asthma

In the early 70's, the effect of macrolides as steroid-sparing agents was proven in a double blind, cross-group clinical trial that compared troleandomycin with placebo groups in 74 patients with severe asthma who were dependent on corticosteroids. Two thirds of the patients reported a clinical improvement with reduction in sputum production, improved pulmonary function, reduced need for bronchodilators, and an improved subjective evaluation of their disease.[63]

In 2005, Cochrane[84] published the results of a review that assessed the data from 7 studies of a total of 416 patients. Only those studies that complied with the following inclusion criteria were evaluated: i) randomized double-blind controlled clinical trials; ii) patients (children or adults) with chronic asthma of varying severity (slight, intermittent, moderate, and severe); iii) treatment with macrolides (clarithromycin in 3 studies, roxithromycin in 2 studies, and troleandomycin in 2 studies) for more than 4 weeks, and iv) evaluation of the asthmatic symptoms and at least one of the following measures of primary pulmonary function: FEV_1, FVC, and peak expiratory flow. The results in FEV_1 show no statistically significant differences between macrolide and placebo groups for the cross-group studies, and the estimated group effect for the 2 parallel group trials was not significant. The FVC results showed no statistically significant differences between the crossed studies. Nor were any significant differences found in corticosteroid consumption. Regarding measurements of secondary results, there was a difference in favour of macrolides in symptom reduction, and in drug tolerability there were no significant adverse episodes as far as gastrointestinal or hepatic function, nor were there significant differences in the withdrawal of patients in different treatment groups. The authors emphasize that in order to correctly interpret the results, one must keep in mind the different types of interventions used, the different types of asthma patients treated (according to severity and chronic infection by *Chlamydia pneumoniae*), and that the measures of the results are heterogeneous between studies. In spite of these limitations, the studies do indicate a certain tendency with respect to the effects of macrolides on the reduction of symptoms and improvement in pulmonary function, improvement in symptom scores, a significant reduction in eosinophilic inflammation markers, and reduction in bronchial hypersensitivity. Additionally, they concluded that due to the small number of patients evaluated, additional studies are needed to establish the efficiency of macrolides to treat this disease, especially in some subgroups of asthma patients, such as those with indications of chronic bacterial infections.

Following this review, several new studies have been published on the application of clarithromycin and azithromycin in asthma patients. Clarithromycin has been studied in 2 randomized double blind clinical trials. In the first of these, 45 patients with severe refractory asthma were randomized to receive 8 weeks of a placebo or clarithromycin (500 mg/12h). The results showed a reduction in IL-8 and the number of neutrophils, but no change in the eosinophil count. These markers increased to baseline levels 4 weeks after suspending treatment. Regarding clinical parameters, there was a decrease in wheezing and improvement in the quality of life indexes for the treated group, but no changes existed in FEV_1 or the response dependant on the dosage of hypertonic saline solution. In the analysis by subgroups (non-eosinophilic asthma), a greater reduction in inflammation markers was observed, as well as a greater improvement in quality of life indicators.[85] The second trial evaluated the effects of clarithromycin (15 mg/kg/day in two applications) during 5 days in 43 children with acute asthma exacerbations. Only the nasopharyngeal concentrations of TNF-α, IL-1β and IL-10 were significantly reduced in the treatment group at 3 months, and the tendency for a greater effect was also observed in patients with evidence of infection by *C. pneumoniae* or *M. pneumoniae*. The microbiological results led the authors to conclude that the immunomodulatory mechanism of clarithromycin must not be completely independent of its activity as an anti-infectious agent for the treatment of asthma. In this study, no differences were found in solution cytokine levels, nor in clinical variables: dyspnoea, cough, rales, wheezing, fever, and asthma rating scale.[86]

Azithromycin has been studied in 2 randomized double blind clinical trials. The first of these, performed on 16 children, showed no significant differences in pulmonary function after 8 weeks of treatment. However, there was a significant reduction in the number of neutrophils and improvement in bronchial hyperactivity post-inhalation of a hypertonic saline solution.[87] In the second study, 45 patients with chronic asthma of varying severity were randomized to receive azithromycin (600 mg/week for a total of 6 weeks [or an equal amount of a placebo]). An improvement was observed in asthma symptoms as well as a decrease in the use of rescue inhalers in the azithromycin group, and these improvements persisted for 3 months following treatment. Elevated baseline anti-*Chlamydia* IgA levels were positively associated with worse asthma symptoms. Although the improvements in asthma symptoms attributable to azithromycin in patients with a high IgA-adjusted dosage was rated 28 compared to 12% in patients with a low IgA-adjusted dosage, this

difference was not statistically significant. Nor was the decrease in anti-*Chlamydia* IgA following treatment.[88]

Chronic Obstructive Pulmonary Disease

The studies of macrolides in COPD have been performed using clarithromycin, azithromycin, and erythromycin. The results generally show an anti-inflammatory effect as shown by: i) reduction in serum and sputum concentrations of cytokines, such as IL-8 and TNF-α,[89,90] and of other mediators, such as lactoferrin, beta-2-microglobulin,[90] mannose-binding lectin, surfactant protein D, and alveolar macrophage mannose receptor,[91,92] and ii) changes in cellular function, such as decreased degranulation and oxidative processes in neutrophils,[89] increased expression of mannose receptors,[91] increased phagocytosis capacity of alveolar macrophages, and a reduction in apoptosis of bronchial epithelial cells.[92] However, these results do not correlate with those from studies by Bernajee et al[93-95] performed with clarithromycin (500 mg/day for 3 months), given that they show no changes in inflammatory cytokine levels or in number of cells in the sputum. However, significant correlations were found in the total number of sputum neutrophils and respiratory symptoms.

Favourable results in clinical responses are scarce, since only the studies by Wilkinson-Seemungal et al[96,97] performed with erythromycin (250 mg/12 h during one year in 109 patients in a randomized double blind study with placebo controls) showed a significant reduction in the incidence of exacerbations in spite of finding no significant differences in FEV_1. Furthermore, no statistically significant differences were found in certain inflammation markers: IL-6, IL-8, and C-reactive protein.

Bronchiectasis

The different studies performed (table 3) using macrolides show improvements in various clinical parameters, and in all of these a decrease in mucus production and purulent sputum features could be appreciated. The improvements in spirometric tests varied between i) the studies that tested an increase in pulmonary function by changes in FEV_1, FVC,[98,99,105] maximum change in forced expired volume in first second (ΔFEV_{1max}),[100] and forced expiratory flow between 25% and 75% o forced vital capacity (FEF_{25-75})[101]; ii) studies that show stabilization of the different parameters[102], and iii) studies that found no differences regarding the pre-treatment FEV_1 values.[100,101] Studies using azithromycin also report on the reduction of exacerbations, necessity of parenteral antibiotics, and hospital readmissions,[99,102,103] as well as reductions in positive sputum cultures in colonized patients.[105] Clinical improvements associated with clarithromycin use would also diminish the number of hospital admissions.[104] Roxithromycin produces a significant increase in the necessary dose of methacholine needed to produce a 20% drop (PD_{20}) in $FEV_{1.}$[100] In inflammation markers, only azithromycin has been shown to decrease IL-8 levels in broncheoalveolar lavage (BAL),[101] while the rest of the markers, such as IL-1, IL-10, TNF-α, and leukotriene B_4 (LTB_4) show no changes.[98,101] On the other hand, neutrophil and macrophage counts show no changes in the sputum,[98] but decreases in BAL do exist.[101]

Bronchiolitis Obliterans Syndrome

The first references to the use of macrolides in this disease are from the 1990's, when Ichikawa et al[106] used erythromycin in low doses (600 mg/day) during 3–4 months in 6 patients with idiopathic bronchiolitis obliterans syndrome not associated with a transplant, obtaining positive clinical, radiological, and physiological results. Based on the results obtained, this therapeutic option (erythromycin [10 mg/kg]) was introduced for post-transplant bronchiolitis, and clinical improvements were observed in pulmonary function parameters such as FEV_1, FVC, diffusing lung capacity for carbon monoxide (DLCO), imaging tests, and a reduction in corticosteroid doses.[107] Later studies (table 4) showed a general improvement in pulmonary function with increases in FEV_1[108-113] and FVC,[110] or at least slowed negative progression of these parameters.[114] However, other studies have not been able to show any clinical benefits.[115]

The correlation between initial neutrophil levels in BAL and the response to treatment stands out. According to this result, a neutrophil count above 15% in BAL has a positive predictive value of 85% in producing a significant response in FEV_1, while neutrophil values below 15% in BAL have a 100% negative predictive value.[112] Other studies place these values at 20% neutrophils in BAL with a negative predictive value of 91%.[113] Furthermore, a fast decrease in FEV_1 before initiating treatment and the use of sirolimus as an immunosupressor for transplants are positive predictors for progression of the disease, while the use of proton pump inhibitors and the response to treatment after 3 months are negative predictors for disease progression.[113]

These clinical benefits could be related to the same mechanisms of action inherent to the macrolides: on the one hand, upon presentation of a certain prokinetic effect, they would diminish gastroesophageal reflux (one of the possible mechanisms of action that contributes to BOS progression)[108] and, similarly, by behaving as an enzymatic inhibitor, they could increase the plasma concentrations

Table 3
Studies performed with macrolides in patients with bronchiectasis

Reference	Study design	No. of patients; mean age (interval ±SD) in years	Drug; posology; mean duration (±SD) in months	Results and comments
Koh et al, 1997[100]	Randomized, double blind, with placebo controls	25; 13 (±2.6)	Roxithromycin; 4mg/kg/12h; 3	Decreased reactivity in the respiratory tract (methacholine test)
Tsang et al, 1999[98]	Randomized, double blind, with placebo controls	21; 54.28 (35–75)	Erythromycin; 500mg/12h; 2	↑ FEV_1 and FVC; decreased volume in sputum
Davies et al, 2004[99]	Prospective open	39; 51.6 (18–77)	AZM; 500mg/day × 6 days, followed by 250mg/day for 6 days and then with 250mg/3 × week; 20 (±10.1)	↓ symptoms and sputum Improved spirometry
Cymbala et al, 2005[102]	Randomized, open, cross-grouped	11; ND	AZM; 500mg/2 times per week; 6	↓ sputum volume
Yalcin et al, 2006[101]	Randomized, with placebo controls	34; 12.5 (9–16)	Clarithromycin; 5mg/kg/day; 3	↓ sputum volume ↓ sputum markers
Anwar et al, 2008[105]	Retrospective, open	56; 63 (±12.9)	AZM; 250mg/day, 3 days per week; 9.1 (±7.5)	↑ FEV_1, decreased frequency of exacerbations Clinically significant reduction in cultures Six withdrawals due to adverse side effects

AZM: azithromycin; SD: standard deviation; FEV_1: forced expired volume in first second; FVC: forced vital capacity; ND: No data.

of certain immunosupressors (tacrolimus) and produce a greater tolerance to allografts with a reduction in the progression of bronchiolitis. However, studies do not show any changes at the gastrointestinal level or in the plasma concentrations of immunosupressors that would support these theories.[109,111,112,114]

Regarding inflammation markers in patients with bronchiolitis obliterans treated with azithromycin, a decrease in serum concentrations of IL-6, monocytes, and CD14,[116] a lower neutrophil count in BAL, decreased IL-8 mRNA values[112], and a reduction in 8-isoprostane oxidative stress factor and phosphorylation of mitogen active protein kinases (p38, c-jun N-terminal kinase and extracellular signal regulated kinase)[117] are all observable.

Relating these results to BOS, macrolides have also been proven to work in organizing pneumonia (previously known as bronchiolitis obliterans organizing pneumonia). Clarithromycin (250 mg/12h for 2 months, followed by 250 mg/24h until completing 3–6 months of treatment) has shown benefits in radiological exams as well as in symptom reduction, although one of these patients withdrew from use of the drug due to adverse side effects. This indicates that clarithromycin may serve as an alternative treatment, especially in those cases where the patient cannot tolerate corticosteroids.[118]

Effects of Treatment with Macrolides on Bacterial Resistance

The long-term use of antibiotics can produce bacterial resistances. In 2006, the first study[119] regarding resistances from long-term use of azithromycin in CF patients was published. This retrospective study over 5 years researched the susceptibility of *S. aureus* and *Haeophilus* sp. to macrolides in CF patients who received long-term azithromycin (500 mg/day 3 days a weeks if> 40 kg or 250 mg if < 40 kg). 155 patients with CF were included in the study, with well-documented cultures (mean age: 11.7 years). Of these, 41% received azithromycin treatment (mean duration: 397 days). In general, the results show that the proportion of cultures positive for *S. aureus* were significantly reduced from 33 to 25%, although the proportion of cultures positive for *H. influenzae* remained stable. All of the CF patients, both those treated with azithromycin and those not, presented a decrease in colonization by *S. aureus* and no change in *Haemophilus* sp.

In the analysis by subgroups, the group treated with azithromycin presented fewer positive cultures, but the proportion of cultures by *S. aureus* that were resistant to the macrolide tested increased directly with long treatments. In contrast, the number of cultures positive for *H. influenzae* resistant to the macrolide tested increased evenly in both groups, although this increase was more marked in the group treated with azithromycin for longer periods of time. These changes proved to be independent of whether or not the patient was a host for *P. aeruginosa*. When comparing the CF group with a control group, the proportion of erythromycin-resistant *S. aureus* increased from 6.9 to 53.8%, while in the control group it remained constant. For *Haemophilus* sp., the values increased from 3.7 to 37.5% and from 9.4 to 26.7%, in the control group.

Tramper et al[120] analyzed sputum cultures obtained from 100 patients with CF colonized by *S. aureus* and their microbial resistances before and during a 3 year maintenance treatment with azithromycin (5–10 mg/kg/day). The results showed that colonization did not decrease significantly after the beginning of treatment, and that compared with pre-treatment levels, where only 10% of patients presented resistant strains to the macrolide tested for (erythromycin), the appearance of resistance increased to 83% during the first year, 97% the second year, and 100% the third year following the start of azithromycin treatment. In respiratory function, FEV_1 improved significantly during the first year of treatment (4.75%), but decreased during the second and third years (5.15 and 3.65%, respectively). However, no statistically significant relationship was found between the appearance of macrolide-resistant *S. aureus* strains and pulmonary dysfunction.

Table 4
Studies performed with macrolides in patients with bronchiolitis obliterans syndrome

Reference	Study design	No. of patients; mean age (interval ±SD) in years	Drug; posology; mean duration (interval) in months	Results and comments
Gerhardt et al, 2003[108]	Open, prospective	6; 39.6 (23–53)	AZM; 250mg/day × 5 days, followed by 250mg/3 × week; 3.19 (1.63–4.76)	↑ FEV_1 of 17,1% (absolute at 0.5l)
Verleden et al, 2004[109]	Open, prospective	8; 36 (5–61)	AZM; 250mg/day for 5 days, followed by 250mg/3 times per week; 5.95 (2.8–8.4)	↑ FEV_1 of 18.3% (absolute at 0.328l) at 12 weeks; of 22.0% (absolute at 0.353l) at 24 weeks; of 33.3% (absolute at 0.533l) at 36 weeks
Khalid et al, 2005[110]	Open, prospective	8; 36 (18–63)	AZM; 500mg/day for 3 days, followed by 250mg/3 times per week; 2.8	↑ FEV_1 of 20.58% (absolute at 280ml) ↑ FVC of 21.57% (absolute at 410 ml). With no adverse side effects
Yates et al, 2005[111]	Retrospective	20; 38 (17–59)	AZM; 250 mg/48h; 3–11	↑ of FEV_1 at 3 months at 110ml
Shitrit et al, 2005[114]	Open, prospective	11; 53.5 (40–67)	AZM; 250mg/3 times per week; 10	No improvement was seen in pulmonary function
Stover et al, 2005[118]	Open, prospective	6; 63.3 (±7.11)	Clarithromycin; 250mg/12h for 2 months, followed by 250mg/24h; 3–6	Patients with bronchiolitis obliterans with organizing pneumonia. Sustained clinical and radiological improvements One withdrawal due to a cutaneous rash
Angel et al, 2006[115]	Open, prospective	8; ND	AZM; non-specified dosage; 12	No improvement was seen in pulmonary function
Verleden et al, 2006[112]	Open, prospective	14; 47.7 (±12.5)	AZM; 250mg/day for 5 days, followed by 250mg/3 times per week; 3	↑ FEV_1, ↓ neutrophils, MRNA and IL-8. Correlation with the results obtained with respect to neutrophils previous to BAL
Gottlieb et al, 2008[113]	Open, prospective	81; 47 (±12)	AZM; 250mg/3 times per week; 16.36 (±5.5)	30% showed improvements at 6 months. Neutrophilia <20%, NPV at 91% for therapeutic failure. Initial FEV_1 and use of inh-mTOR (sirolimus and everolimus) as positive predictors for disease progression. PPI and response at 3 months negative predictors for disease progression

mRNA: messenger ribonucleic acid; AZM: azithromycin; BAL: bronchioalveolar lavage; SD: standard deviation; FEV1: forced expired volume in first second; FVC: forced vital capacity; PPI: Proton pump inhibitors interleukin; inh-mTOR: mammalian target of rapamycin; ND: no data; NPV: negative predictive value.

Kasahara et al[121] retrospectively studied the influence of long-term macrolide treatment with erythromycin (600 mg/day, mean treatment duration: 4.3 years), or clarithromycin (400 mg/day, mean treatment duration: 4.1 years) in various respiratory diseases (DPB, bronchiectasis, emphysema, and bronchitis) in 57 patients (31 with clarithromycin and 26 with erythromycin) and their effects on *S. pneumoniae* sensitivity. The results indicated that all isolates from the clarithromycin group and from 25 of the 26 patients of the erythromycin group showed *in vitro* resistance to the macrolide tested.

Finally, Hansen et al[122] showed that long-term treatment (mean treatment time of 4.0 years) with low doses of azithromycin (250 mg/day if > 40 kg or 250 mg on alternate days if ≤ 40 kg) in 70 patients reduced the prevalence of sputum growth of *S. aureus*, *S. pneumoniae* and *H. influenzae*, but increased the resistance of *S. aureus* to the macrolide tested, although it did not report any clinical significance. In contrast with previous studies, no resistances were found in *H. influenzae* or in *S. pneumoniae*, and only one culture of *Moraxella catarrhalis* showed macrolide resistance.

Conclusions

The use of macrolides can be considered as a complement to current treatments for various respiratory diseases whose physiopathological substrate is an inflammatory mechanism. The clinical results obtained in diseases such as DPB and CF have permitted its use to be extended to other diseases, such as bronchiectasis, COPD, asthma, or bronchiolitis obliterans.[123] Other respiratory diseases that could benefit from this treatment would be bronchiopulmonary dysplasia[124] or desquamative interstitial pneumonia.[125]

However, the use of macrolides is not only based on the treatment of respiratory diseases, taking into account that its use has been extended to other illnesses, such as chronic sinusitis,[126-128] coronary artery disease,[129] rosacea, and psoriasis,[130-133] Crohn's disease,[134-136] and in the treatment of arthritis, undifferentiated connective tissue disease, and progressive recurrent multifocal osteomyelitis.[137-140]

In spite of the possible clinical benefits provided by this treatment, basic questions still require answers, such as the safety and efficacy of the treatment. Indeed, this is a case of a treatment for long-term use, although the optimal duration of treatment has not been formally studied for the majority of applicable diseases, making the length of time for administration a judgement call for the responsible clinician, a choice always to be made based on the patient's evolution and personal experience. Furthermore, the long-term use of antibiotics is not without its collateral effects on the microbial resistance of pathogens that usually colonize the respiratory tract. How could the changes in bacterial flora resistance patterns (due to the use of macrolides) affect the treatment of exacerbations of diseases that require antibiotic treatment? What effects could these have on the evolution of the disease itself? These are questions that remain answered. Another unresolved uncertainty is the choice of the most suitable macrolide. This is a question that must be resolved in as yet not performed comparative studies.

Regarding the efficacy of treatment, the studies support the use of erythromycin in DPB (improved long-term survival of the population). In CF, the use of azithromycin appears to be the most reasonable choice since the different studies presented (randomized double-blind clinical trials with placebo controls) show certain benefits that could justify its use. However, the identification of patient subgroups that could potentially benefit from treatment requires new clinical studies or trials.

A more debatable topic would be the use of macrolides in other types of diseases, for reasons such as: i) the scarcity of results with clinical relevance (COPD, bronchiectasis and asthma); ii) the discrepancies between them (BOS); iii) the fact that they have been retrospective or prospective studies with small numbers of patients; iv) the description of sporadic clinical cases, or v) only the effects from *in vitro* treatment outside the range of normal use are described in many cases, which compromises the validity of the results and the level of recommendation for generalized macrolide use as anti-inflammatories. As a result, new studies are required before their recommendation in clinical practice can be suggested for this type of diseases as in non-respiratory illnesses.

We hope that these studies and future ones will add to the validity needed in order to make a decision regarding the convenience or lack thereof of the use of macrolides as an efficient anti-inflammatory treatment.

Conflict of Interest

The authors affirm that they have no conflicts of interest.

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