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Long-term macrolide treatment for chronic respiratory disease

Paolo Spagnolo[1], Leonardo M. Fabbri[1], Andrew Bush[2]

[1] Section of Respiratory Diseases, Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Policlinico di Modena, Italy, [2] Imperial College and Royal Brompton Harefield NHS Foundation Trust, London UK.

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Corresponding author: Paolo Spagnolo

Tel: 0039 059 4225824

FAX: 0039 059 4224231

E-mail address: paolo.spagnolo@unimore.it

Abstract

Long-term macrolide treatment was first shown to alter the natural history of diffuse panbronchiolitis (DPB) in the late ‘80s. Since then, macrolides have been demonstrated to exert anti-inflammatory and immunomodulatory activity in addition to being antimicrobial. Indeed, their spectrum of action extends to regulation of leukocyte function and production of inflammatory mediators, control of mucus hypersecretion, resolution of inflammation, and modulation of host defence mechanisms. As such, the potential benefit of macrolide antibiotics has been evaluated in a variety of chronic respiratory diseases. The best studied condition is cystic fibrosis (CF), in which there have been six randomized controlled trials showing evidence of benefit. However, most of the studies were limited by the small number of patients and the short follow-up. More recently, landmark studies have demonstrated the efficacy of azithromycin in reducing the risk of acute exacerbations in patients with chronic obstructive pulmonary disease (COPD), but optimal duration and dosing of macrolide treatment remain uncertain.

With the exception of patients with DPB and CF, until clear evidence of efficacy is available, the long-term use of macrolide should be limited to highly selected patients after careful evaluation of benefit and harm, or in the context of randomized controlled clinical trials.

Keywords: airway disease, asthma, chronic obstructive pulmonary disease, cystic fibrosis, infection, macrolides

Introduction

Macrolide antibiotics (commonly referred to as “macrolides”) belong to a family of compounds chemically characterized by the presence of a macrocyclic lactone ring of 12 or more elements [1]. Given their favorable bioavailability via the oral route, excellent tissue penetration, and broad efficacy against many lung pathogens (most Gram-positive and some Gram-negative bacteria, mycobacteria, *Chlamydia*, *Mycoplasma* and *Legionella* species), macrolides are widely used as first-line agents in the therapy of respiratory infections [2], although there is a concern that long-term administration of macrolides can promote antimicrobial resistance [3]. In recent years, there has been an increasing interest in the potential immunomodulatory properties of macrolides following the observation of the effectiveness of erythromycin in diffuse panbronchiolitis (DPB), an idiopathic disease found almost exclusively in the Far East and characterized by chronic recurrent bronchiolitis, and peribronchiolitis with inflammatory infiltration of the small airways [4]. The immunomodulatory effects of macrolides, which are only seen with 14- (erythromycin, clarithromycin and roxithromycin) and 15-members (azithromycin) [5], may take several weeks to manifest, and include reduced airway mucus secretion and viscosity [6] and decreased airway neutrophil accumulation through a reduction in pro-inflammatory cytokines expression, and adhesion molecule production [7-9] (Figure 1).

Collectively, these observations provided the rationale for a number of studies performed over the last decade to assess the efficacy of macrolides in chronic respiratory diseases other than DPB, such as cystic fibrosis (CF), asthma, chronic obstructive pulmonary disease (COPD), non-CF bronchiectasis, and bronchiolitis obliterans syndrome (BOS) [10]. The purpose of this review is to summarize and discuss the potential for macrolide therapy in chronic respiratory diseases in the light of the data provided by recently concluded large clinical trials.

Search strategy and selection criteria

We conducted a literature search using the Pubmed/MEDLINE and EMBASE databases. We used the terms “macrolide” OR “erythromycin” OR “clarithromycin” OR “azithromycin” OR “roxithromycin” OR “troleandomycin” OR “telithromycin” in combination with the terms “asthma”, “bronchiectasis”, “cystic fibrosis”, “diffuse panbronchiolitis”, “bronchiolitis obliterans”, “chronic rhinosinusitis”, “chronic obstructive pulmonary disease”, “COPD”, “organizing pneumonia”, “acute lung injury” and “respiratory viral infections”. Our review includes only publications in the past 3 years and is not limited to double-blind placebo-controlled studies.

Diffuse panbronchiolitis

Diffuse panbronchiolitis (DPB) is a progressive inflammatory airway disease reported almost exclusively in East Asians and characterized by chronic airway infection - often complicated by *Pseudomonas aeruginosa* (*P. aeruginosa*) infection - chronic productive cough, dyspnea, airflow limitation, and chronic sinusitis [11, 12]. The term "diffuse" refers to the distribution of the lesions throughout both lungs, while "pan-" refers to the inflammatory involvement of all layers of the respiratory bronchioles. Radiographic findings include reticulo-nodular infiltrates, while high-resolution computed tomography (HRCT) scans show the characteristic centrolobular nodules with a “tree-in-bud” appearance (Figure 2). Bronchoalveolar lavage fluid (BALF) obtained from DPB patients reveals high levels of neutrophils and lymphocytes as well as of interleukin (IL)-8 and other proinflammatory cytokines and chemokines [13, 14], suggesting a chronic inflammatory process further exacerbated by the presence of pathogens.

Kudoh and colleagues were the first to demonstrate in a large retrospective study that low-dose erythromycin (EM) not only ameliorated the signs and symptoms of DPB but also improved survival [4]. These unexpected results were attributed to a previously unknown antiinflammatory effect of EM rather than to its antimicrobial properties. In fact, EM 600 mg daily for a month has been shown to reduce the number of neutrophils and the concentration of IL-8 in BALF of DPB

patients regardless of *P. aeruginosa* infection [15]. In addition, the maximal serum and sputum levels of EM have been reported to be below the minimum inhibitory concentration (MIC) of the relevant pathogens (*H. influenzae* and *P. aeruginosa*), thus confirming that it is unlikely that the beneficial effect of EM in DPB purely results from its antibacterial activity [16].

Other macrolide antibiotics which proved effective in DPB include roxithromycin, clarithromycin, and azithromycin [17-19]. The treatment of DPB is the most striking example of the benefits of macrolides in chronic respiratory diseases with the 10-year survival rate increasing from 12-50 % (depending on whether patients were infected with *P. aeruginosa*) to > 90% since the introduction of macrolide therapy [4, 20]. So successful has this treatment been that it is impossible nowadays to conduct a randomized controlled trial, since no patient will agree to be randomized to placebo. Nevertheless, the authors of a recent systematic review evaluating the effects of macrolides in DPB identified only one small and of poor methodological quality randomized controlled trial (RCT) [21] and concluded that the use of macrolides in DPB is based on non-RCTs or retrospective studies [22]

Cystic fibrosis

Cystic fibrosis (CF) - the most common life-shortening inherited disease in white populations (1 in 2500 newborns in white races) - is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [23]. Alterations in epithelial cell ion transport resulting from defective CFTR lead to increased sputum viscosity, stasis of secretions, impaired muco-ciliary clearance, recurrent respiratory infections, and chronic progressive bronchiectasis, in a vicious circle (Figure 3) [24]. In CF, abnormal CFTR function affects a number of organs, but involvement of the airways has the most dramatic impact on quality of life and survival [25]. Characteristic organisms associated with airway infection in patients with CF are, most notably, *Staphylococcus aureus* (*S. aureus*) in the early course of the disease and *P. aeruginosa* at a later stage [26]. However, there is increasing appreciation that the lower airways of CF patients harbor communities

of bacteria far more complex than previously thought and which include, amongst others, *Stenotrophomonas maltophilia*, isolates of the species *Burkholderia cepacia*, non-tuberculous mycobacteria, fungi and viruses [27-29].

The airway inflammatory response in CF is characterized by neutrophilic infiltration and pro-inflammatory cytokine production. This has been demonstrated even in the absence of bacterial infection, suggesting that airway inflammation may precede bacterial infection [30]; however, it remains controversial whether the CF airway is intrinsically pro-inflammatory in the absence of infection, or whether there is solely an augmented inflammatory response in the presence of inflammation. The possibility that macrolides might modify the neutrophilic inflammatory response in CF was first investigated in the early 2000s. Since then, a number of clinical trials have confirmed their beneficial effects both in adults and children [31-37]. Recently, in a multicenter, randomized, double-blind, placebo-controlled trial, 260 CF patients uninfected with *P. aeruginosa* were randomized in a 1:1 ratio to azithromycin (AZM) 250 or 500 mg (based on body weight) three days per week, or placebo for 24 weeks. Azithromycin treatment did not improve pulmonary function, suggesting that the beneficial effect of AZM in CF is mainly due to its activity against *P. aeruginosa* [36]. However, it should be noted that the vast majority of the recruited patients had very good lung function (mean FEV_1 nearly 100% in both groups) thus reducing the chance of improving lung function with any intervention. This group also reported the effects of AZM on airway inflammation. They measured serum absolute neutrophil count, high sensitivity C-reactive protein (HsCRP), myeloperoxidase, serum amyloid A (SAA), and calprotectin and demonstrated a significant decreased from baseline to Day 28 in the azithromycin group. The effects on neutrophil count, SAA and HsCRP were still present at the end of the study at Day 168. There were some correlations between individual inflammatory parameters and weight and spirometric changes, but in our view, these data did not show any consistent picture suggestive that these were really important changes [38]. Azithromycin has no direct bactericidal effect on *P. aeruginosa*, but may reduce the organism virulence by altering biofilm formation, decreasing bacterial adherence to

epithelial cells, inhibiting bacterial motility, or acting synergistically with other antibiotics [39]. However, further analysis of this same dataset showed that in patients not infected with *P. aeruginosa*, azithromycin significantly reduced neutrophil counts and serum inflammatory markers within 28 days of initiating treatment [38]. As such, the mechanism/s by which macrolides exert their beneficial effect in CF (antimicrobial activity, immunomodulation, or both) remains to be determined. However, a recent Cochrane systematic review and meta-analysis of data from high-quality clinical trials provides compelling evidence that long-term macrolide therapy improves lung function, reduces the risk of infective exacerbations, decreases the requirement for additional antibiotics and improves nutritional measures in patients with CF, although it is unclear whether the clinical benefits may be maintained in the longer term, beyond 12 months [40]. Treatment with AZM was associated with reduced isolation of *S. aureus* on respiratory culture, and no change in prevalence of atypical mycobacteria, but also with a significant increase in macrolide bacterial resistance. Adverse events were uncommon and not obviously associated with AZM, although a once-weekly high dose regimen was associated with more frequent gastrointestinal adverse events. Macrolide antibiotics other than AZM have either been evaluated in underpowered studies - mostly reported in abstract form - or have been shown to be ineffective in patients with CF. Robinson and colleagues performed a 12-month double-blind, cross-over trial in which 63 patients were randomly assigned to receive 500 mg oral slow release clarithromycin or placebo once daily [41]. Fifty-two patients completed the study. No significant difference in either the primary efficacy end point (change in lung function during the study period) or any secondary end points, including, amongst others, number of pulmonary exacerbations and sputum inflammatory cytokine content was observed during the study period between the treatment and placebo arms.

However, in summary,, CF is the disease outside DPB for which there is most evidence for sustained benefit from macrolide therapy.

Non-CF bronchiectasis

The effectiveness of long-term macrolide therapy in DPB and CF has provided the rationale for using these agents in patients with bronchiectasis not caused by CF (commonly referred to as *idiopathic* bronchiectasis, although often the cause of the bronchiectasis is known, such as ciliary dyskinesia, allergic bronchopulmonary aspergillosis or post-infectious) (Figure 4). Regardless of cause, bronchiectasis involves a vicious cycle of infection leading to airway inflammation and lung damage [42]. The airway inflammatory response is characterized by an intense cellular infiltrate with mononuclear cells ($CD4^+$ T lymphocytes and macrophages), a prominent neutrophilia and increased IL-8 expression [43]. According to the "vicious cycle hypothesis", if infection is the primary driver of airway inflammation, bacterial clearance through the use of short- or long-term antibiotic therapy would be expected to reduce airway inflammation, allow airway healing and modify the long term course of the disease. Until very recently, the role of macrolide therapy in non-CF bronchiectasis had only been investigated in studies that were small, of short duration and not assessing clinically relevant outcomes such as pulmonary exacerbations and quality of life [44-47]. In a recently published randomized, double-blind, placebo-controlled trial, 141 patients (18 years or older) with a diagnosis of bronchiectasis as defined by HRCT and at least one pulmonary exacerbation requiring antibiotic treatment in the previous year, were assigned to receive in a 1:1 ratio azithromycin (500 mg three times per week) or placebo for 6 months [48]. The rate of event-based exacerbations, one of the primary endpoints, was 0.59 per patient in the azithromycin group and 1.57 per patient in the placebo group in the 6-month treatment period ($p<0.0001$). Conversely, prebronchodilator FEV_1 and St George's respiratory questionnaire total score - both co-primary endpoints - did not differ significantly between the azithromycin and placebo groups.

Given the small number of studies, most of which with small number of patients, the role of long-term macrolide therapy in non-CF bronchiectasis remains unclear thus questioning the hypothesis that antibiotics can "break the cycle", and highlighting the difficulty in extrapolating from CF studies to non-CF bronchiectasis. As such, chronic macrolide therapy for this condition cannot be

routinely recommended. On the other hand, azithromycin may represent a therapeutic option in selected patients, i.e., those with a history of frequent exacerbations.

Asthma

Asthma is an airway disease characterised by chronic inflammation, bronchial hyperresponsiveness, and airflow limitation, which clinically manifests with recurrent cough, wheezing, chest tightness, dyspnea, and mucus production [49]. The mechanisms responsible for the maintenance of the inflammatory response, which is characterized by increased numbers of activated lymphocytes, eosinophils, and variably increased mast cells, are only partially known, but a growing body of evidence suggests that chronic or subacute infection with atypical bacteria, such as *Mycoplasma pneumoniae* (*M. pneumoniae*) and *Chlamidophila pneumoniae* (*C. pneumoniae*) may be an important contributor to both disease pathogenesis and severity in some patients [50]. Indeed, the very nature of infection caused by these agents - a chronic intracellular inflammatory process in the case of *C. pneumoniae*, and persistent epithelial damage in the case of *M. pneumoniae* - makes them ideal candidates to produce chronic symptoms and poor asthma control.

The possibility of chronic infection with organisms that are sensitive to macrolides provides a strong rationale for their use in asthma, although macrolides may also function as steroid-sparing, or anti-inflammatory agents [51, 52]. Early studies have reported conflicting results [53-57] Recently, Sutherland and co-workers evaluated the effect of 16 weeks of either clarithromycin or placebo, added to fluticasone, on asthma control in individuals with or without lower airway polymerase chain reaction (PCR) evidence of *M. pneumoniae* or *C. pneumoniae* [58]. Due to the small number of patients with PCR positivity (12/92), the two groups were combined for the analysis. The addition of clarithromycin did not improve asthma control or lung function for the entire group, suggesting that the routine addition of macrolide therapy to uncontrolled asthmatics on low-dose inhaled corticosteroids offers little additional benefit.

Interpretation of the studies as a whole is difficult owing to the heterogeneity of the study populations, the small number of patients, and the relatively short treatment duration in most studies (≤ 12 weeks). This was also reflected in a Cochrane review, which concluded that there is insufficient evidence to support or refute the use of macrolides in the treatment of asthma [59].
The evidence for benefit of macrolides in paediatrics is even scantier. Of note, a study which compared azithromycin with montelukast in children with asthma still symptomatic despite inhaled corticosteroids and long-acting β_2-agonists ended in futility. This was because most children who were assessed either did not have asthma or were not taking their treatment, underscoring the need to get basic management steps right before escalating medical therapy [60].
At present there is little evidence to justify routine long-term use of macrolides in asthma. However, a subgroup of patients, i.e., those with evidence of atypical bacterial infection in the airways, may benefit from macrolide treatment

Chronic obstructive pulmonary disease

COPD is the fourth leading cause of death worldwide [61]. Contributing substantially to the morbidity and mortality of patients with COPD are episodes of increased respiratory and systemic symptoms - commonly caused by airway bacterial and viral infections - referred to as acute *exacerbations* (AECOPD). Each year, on average, up to one third of patients with COPD experience one or more exacerbations [62], which represent a major cause of primary care visits, hospital admission, impaired health status and mortality [63, 64]. In addition, acute exacerbations account for a substantial percentage of the cost of treating COPD [65]. As such, reduction of these events has become a major goal in the development of new therapeutic strategies for COPD.
Inhaled corticosteroids, long-acting β_2-agonists, long-acting muscarinic antagonists, as well as roflumilast - an oral, selective phosphodiesterase type-4 inhibitor - have all been shown to reduce the frequency of acute exacerbations of COPD [66-70], but these strategies appear to reduce AECOPD at best by 40% [71].

It has been speculated that alternative approaches that directly address the infectious and inflammatory aspects of AECOPD (i.e., the use of antibiotics prophylactically) might have a significant additional benefit in terms of exacerbation reduction [72]. A number of studies have evaluated whether long-term macrolide treatment decreases the risk of AECOPD with conflicting results [73-79]. More recently, in a prospective, parallel-group study, 1142 patients with COPD at increased risk of exacerbation were randomly assigned in a 1:1 ratio to receive azithromycin (n = 570) at a dose of 250 mg daily or placebo (n = 572) for one year in addition to their usual care [80]. The median time to the first acute exacerbation of COPD (the primary outcome) was 266 days in the azithromycin group as compared with 174 days in the placebo group ($p = <0.001$). In addition, azithromycin treatment decreased the frequency of AECOPD ($p = 0.01$) and the incidence of colonization with selected respiratory pathogens and improved quality of life, but was associated with an increased incidence of colonization with macrolide-resistant organisms and decreased hearing.

Chronic bacterial colonization of the lower airways perpetuates inflammation and contributes to the progression of COPD [81]. In turn, inflammation makes the lungs of COPD patients more susceptible to infections, both acute and chronic. Although their precise mechanisms of action (anti-infective, anti-inflammatory or both) are incompletely understood, macrolides have the potential to break the vicious circle of infection-inflammation and strengthen lung defenses in COPD patients at increased risk of exacerbations. Until clearer evidence of efficacy and safety is available, routine use of azithromycin prophylaxis for preventing acute exacerbations is not recommended due to an unfavourable balance between benefits and side effects [82]. However, it may be considered for individual severe COPD patients with frequent exacerbations despite best quality, guidelines-based treatment, in those who are not at high risk of cardiovascular complications, with close monitoring of hearing, and after careful review of all medications in order to avoid any potential adverse interactions [80]

Post-transplant bronchiolits obliterans syndrome

Bronchiolitis obliterans syndrome (BOS) - one of the most common and severe non-infectious pulmonary complications of chronic rejection (lung or bone marrow) - is characterized by an inflammatory response of terminal and respiratory bronchioles ultimately leading to scarring and total occlusion of the conducting airways [83] (Figure 5). Given the substantial morbidity and mortality associated with BOS combined with the limited effectiveness of traditional anti-rejection therapy, and based on the similarities with other bronchiolar disorders, there has been recent interest in the potential role of macrolides in the management of post-transplant BOS.

The efficacy of azithromycin (250 mg thrice weekly for an average of 16 months) was evaluated in a large observational study of lung transplant patients; 24/81 (30%) showed improvement in FEV_1 after 6 months, but 22 of the 24 responders improved after only three months of therapy [84]. Of note, responders at 6 months had higher pre-treatment BAL neutrophil count, with a cut-off value of <20% having a negative predictive value of 0.91 for treatment response. Similar results had been reported by Verleden and colleagues [85]. These studies revealed a dichotomy in the clinical spectrum of BOS, with neutrophilic (partially) reversible allograft dysfunction being macrolide responsive, while fibroproliferative BOS is not [86]. Azithromycin treatment has also been associated with increased survival. In a large retrospective cohort study of lung transplant recipients (n = 178), this beneficial effect was more pronounced when treatment was initiated during BOS stage 1 [87].

The potential role of azithromycin in halting progression in patients with bronchiolitis obliterans syndrome is intriguing. However, long-term randomized placebo-controlled clinical trials are required before routine use of this therapy.

Chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is the second most prevalent self-reported chronic condition in the United States, affecting approximately 15% of the population [88]. CRS, which is characterized by

hyperplasia, hypertrophy, and hypersecretion of the nasal and paranasal sinus mucosa, is diagnosed when symptoms of acute RS persist for more than 12 weeks. Long-term macrolide therapy has been shown to improve symptoms, shrink the size of nasal polyps, and decrease the levels of pro-inflammatory cytokines in patients with CRS, although mainly in small, open-label studies [89-92]. As with other diseases, the mechanisms behind this beneficial effect are unclear and may relate to the ability of macrolides to inhibit the local host immune response rather than via their antimicrobial properties [93, 94].

However, a recent study including 60 patients with recalcitrant CRS (with and without nasal polyps) unresponsive to optimal medical or surgical treatment, reported no significant differences in symptom scores or objective measures after a 3-month course of azithromycin as compared to placebo [95], highlighting the need for matching patient characteristics, drug administered and outcome measures before comparing the results of different studies.

Despite the potential interest of this therapeutic approach, current guidelines do not recommend macrolide treatment as standard therapy in CRS [96]. In addition, because of the concern for an increasing incidence of macrolide-resistant bacterial strains, repeated nasal cultures should be performed in patients on long-term macrolide therapy.

Other conditions

Recent experimental observations, mostly based on animal models, suggest that macrolide use may be beneficial in a number of other chronic respiratory diseases, particularly diffuse parenchymal lung disease and lung fibrosis [97]. In fact, macrolides are thought to take part to the reparative response of alveolar epithelium to injury - by acting on several components of the regenerative process - and to lipid metabolism and alveolar surfactant homeostasis [98]. However, at present, clinical evidence of efficacy in these conditions is limited to case reports or small case series.

Organizing pneumonia. Organizing pneumonia (OP) is an inflammatory disorder affecting the distal airways and alveoli characterized histo-pathologically by intra-alveolar buds of granulation

tissue, consisting of intermixed myofibroblasts and connective tissue. The disease can be either *idiopathic* (cryptogenic organizing pneumonia, COP) or associated with a number of entities, such as infections, drug toxicity, connective tissue disease, vasculitis, hematologic malignancies, organ transplantation, radiation therapy, eosinophilic pneumonia and many others [99]. Stover and Mangino reported on six patients (three with COP and three with OP secondary to radiation therapy) who responded to clarithromycin [100]. The authors suggest considering long-term macrolide therapy in patients with minimal symptoms and/or minimal physiologic impairment, as adjuvant therapy in patients receiving steroids, or in those who cannot tolerate steroids. The beneficial effect of macrolides in OP is thought to be due to their inhibitory effect on IL-8 release and neutrophil accumulation in the peripheral airways [101]. However, which patients are likely to respond to macrolide therapy and the appropriate dose and duration of treatment are unknown. As such, the decision to use macrolides in OP should be made on a case-by-case basis. At present, corticosteroids represent the treatment of choice for COP.

Acute lung injury. Acute lung injury (ALI) is a syndrome of acute inflammatory pulmonary edema poorly responsive to pharmacological treatment and with a mortality rate of 30% to 40% [102]. Recently, in a secondary analysis of a large multicenter clinical trial dataset, Walkey and Wiener evaluated the association between macrolide use and mortality in patients with ALI [103]. Among patients who received a macrolide antibiotic (47/235, 20%), erythromycin was the most common (57%), followed by azithromycin (40%) and clarithromycin (3%). The median duration of macrolide therapy was 4 days. Eleven of the 47 patients (23%) who received macrolides died as compared to 67 of the 188 (36%) who received a non-macrolide antibiotic (either fluoroquinolone or cephalosporin; $p = 0.11$). In addition, macrolide use was associated with lower 180-day mortality ($p = 0.028$) and shorter time to successful discontinuation of mechanical ventilation ($p = 0.009$). Interestingly, subjects administered macrolides were more likely to have pneumonia as an ALI risk factor. In contrast, fluoroquinolone and cephalosporin use was not associated with improved

outcomes. These findings suggest that macrolide antibiotics hold promise as a potential therapy early in the course of ALI.

Respiratory viral infections. Bronchiolitis is a serious, potentially life-threatening respiratory illness that often affects young babies. It frequently occurs in the first year of life and represents the most common cause of hospital admission in babies under the age of six months [104]. Babies usually present with runny nose, cough, shortness of breath and signs of respiratory distress. Respiratory syncytial virus (RSV) is the most common pathogen identified but other viruses such as human meta-pneumovirus (HMPV), influenza, parainfluenza, adenovirus and rhinovirus have also been implicated [105]. The disease is poorly responsive to treatment, including antiviral drugs. Since viruses are potent inducers of cytokine and chemokine production and release [106], the potential benefit of macrolide anti-inflammatory and immunomodulatory activities has also been evaluated in respiratory viral infections, though in small studies and with conflicting results.

In a double-blind, randomized, placebo-controlled trial, Tahan and colleagues evaluated the efficacy of clarithromycin given daily for 3 weeks at the dose of 15 mg/Kg in infants younger than seven months hospitalized for RSV bronchiolitis [107]. Nine subjects were excluded from analysis due to corticosteroid use leaving 12 in the clarithromycin group and nine in the placebo group. Clarithromycin treatment was associated with a statistically significant reduction in the length of hospital stay, duration of oxygen use, need for β_2-agonists, and readmission to the hospital within 6 months after discharge. Significant decreases in plasma IL-4, IL-8, and eotaxin levels were also observed in the clarithromycin group. However, a subsequent larger randomized, placebo-controlled trial of infants (n = 71) younger than 24 months admitted to hospital for clinically-suspected viral bronchiolitis found that azithromycin (10 mg/Kg/day) was not superior to placebo with regard to length of hospital stay (the primary outcome), days of symptoms, duration of fever, bronchodilator use, and need for supplemental oxygen [108]. As such, a recent Cochrane review found minimal evidence in support of the use of macrolides in infants with bronchiolitis [109]. Finally, Sawabuchi and colleagues have recently shown that the addition of clarithromycin to

oseltamivir augmented secretory (s)IgA production and restored local mucosal sIgA levels in children with acute influenza, suggesting a boosting effect on the nasopharyngeal mucosal immune response in children with influenza A [110].

Risks of long-term macrolide treatment

Three major categories of adverse effects may complicate long-term use of macrolides: ototoxicity, cardiac toxicity, and drug-drug interactions. Albert and colleagues reported an excess rate of hearing decrements of approximately 5% attributable to azithromycin use [80]. Ototoxicity following long-term azithromycin therapy has also been reported in patients with disseminated *Mycobacterium avium* disease [111]. Of note, replacement of azithromycin with clarithromycin in the treatment regimen led to complete recovery in patients previously complaining of hearing loss. Macrolides prolong the QTc interval [112], which, in turn, increases the risk of *torsades de pointes*, potentially resulting in ventricular fibrillation and sudden death. This risk is particularly high in older COPD patients who are more likely to both have cardiac disease and be taking other drugs that prolong the QTc interval. Although erythromycin and clarithromycin have been most commonly associated with cardiac arrhythmias [113], azithromycin should also be avoided in subjects with a high risk of baseline cardiovascular disease [114]. Macrolides also inhibit the CYP3A4 isoenzyme, resulting in increased serum levels of other drugs metabolized by this enzyme, such as statins, warfarin and amiodarone.

Reduced susceptibility of respiratory pathogens to macrolides has increased considerably over the last decade [115]. A similar increase has also been observed in the oro-pharyngeal carriage of macrolide-resistant commensals, which, though usually harmless, can cause infection in immunocompromised hosts, or transfer the resistance acquired to other pathogens [116]. Data from studies in patients with CF suggest that macrolides resistance of respiratory pathogens, particularly *S. aureus*, increases significantly when maintenance therapy is given for long period of time (3-5 years), though without apparent adverse consequences for the treatment of subsequent acute

exacerbations [117-119]. A related concern is the potential wider spread of macrolide-resistant organisms from patients being treated prophylactically to both the general population and patients with diseases - such as non-tuberculous mycobacteria (NTM) diseases - for which macrolides are commonly used. In this regard, ongoing research is exploring the possibility to develop macrolides that lack antimicrobial properties but retain the immunomodulatory properties, thus decreasing the risk for antimicrobial resistance to develop.

A number of recent studies have also identified an increase in mycobacterial infection of CF patients, predominantly with the multi-drug-resistant highly pathogenic NTM *Mycobacterium abscessus* [120, 121]. Renna and colleagues demonstrated that azithromycin *paradoxically* inhibits intracellular killing of mycobacteria by blocking autophagy, a critical cell homeostatic process that protects against infectious, autoimmune and inflammatory diseases [122].

Concluding remarks

The introduction of chronic low-dose macrolide therapy for the treatment of DPB has dramatically altered the natural history of this disease. Based on this observation, the interest in the potential use of macrolides for the treatment of chronic respiratory disease has greatly increased, and a number of studies are currently underway (http://clinicaltrials.gov/ct2?term=macrolides+AND+chronic+respiratory+diseases&Search=Search). In fact, owing to their immunomodulatory and antimicrobial properties together with the high concentrations achieved in the respiratory tract tissues and extracellular fluids, macrolides represent ideal candidates for the management of lung diseases with a chronic inflammatory and infectious component [123]. The best evidence for the chronic use of macrolides is in CF. For some of these disorders, such as asthma and non-CF bronchiectasis, scientific evidence to justify the routine use of macrolides is controversial. Conversely, recent data from large clinical trials in COPD, a disease characterized by increased pulmonary inflammation at baseline, frequent bacterial colonization/infection, and recurrent exacerbations, which further increase lung inflammation,

suggest a beneficial effect of macrolide prophylaxis in patients at high risk of exacerbations. Nevertheless, which patients are likely to respond to macrolide therapy, the appropriate dose (once daily, three times weekly or once weekly) and duration of treatment are unknown. As such, the decision to use macrolides, with the exception of DPB (and probably also CF) should be made on a case-by-case basis. The extent of benefits must be set against the risks of increased bacterial resistance and whether benefits are maintained over the long term needs to be elucidated. As such, additional studies are needed before macrolides become established part of routine therapy in clinical practice other than in DPB and CF.

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Figure legends

Figure 1. Potential beneficial effects of macrolides in chronic respiratory diseases. Macrolides inhibit bacterial protein synthesis, reduce bacterial adherence and bacterial toxin production, inhibit biofilm function, and reduce generation of oxygen-free radicals, which result in **reduced bacterial load and virulence**; macrolides can also modulate mucin gene expression and mucin protein production, and suppress *quorum sensing* proteins with **reduced airway secretion** and **improved muco-ciliary clearance**. Finally, macrolide antibiotics exert several anti-inflammatory and immunomodulatory activities, including decreased neutrophil chemotaxis and survival, down-regulation of adhesion molecule expression, increased alveolar macrophage phagocytosis of apoptotic cells, down-regulation of adesion molecule expression, inhibition of transcription factors leading to decreased pro-inflammatory cytokine production, increased β-defensin levels, reduced oxygen species production, reduction of T cell number and migration, and modulation of dendritic cell function, thus attenuating chronic inflammation.

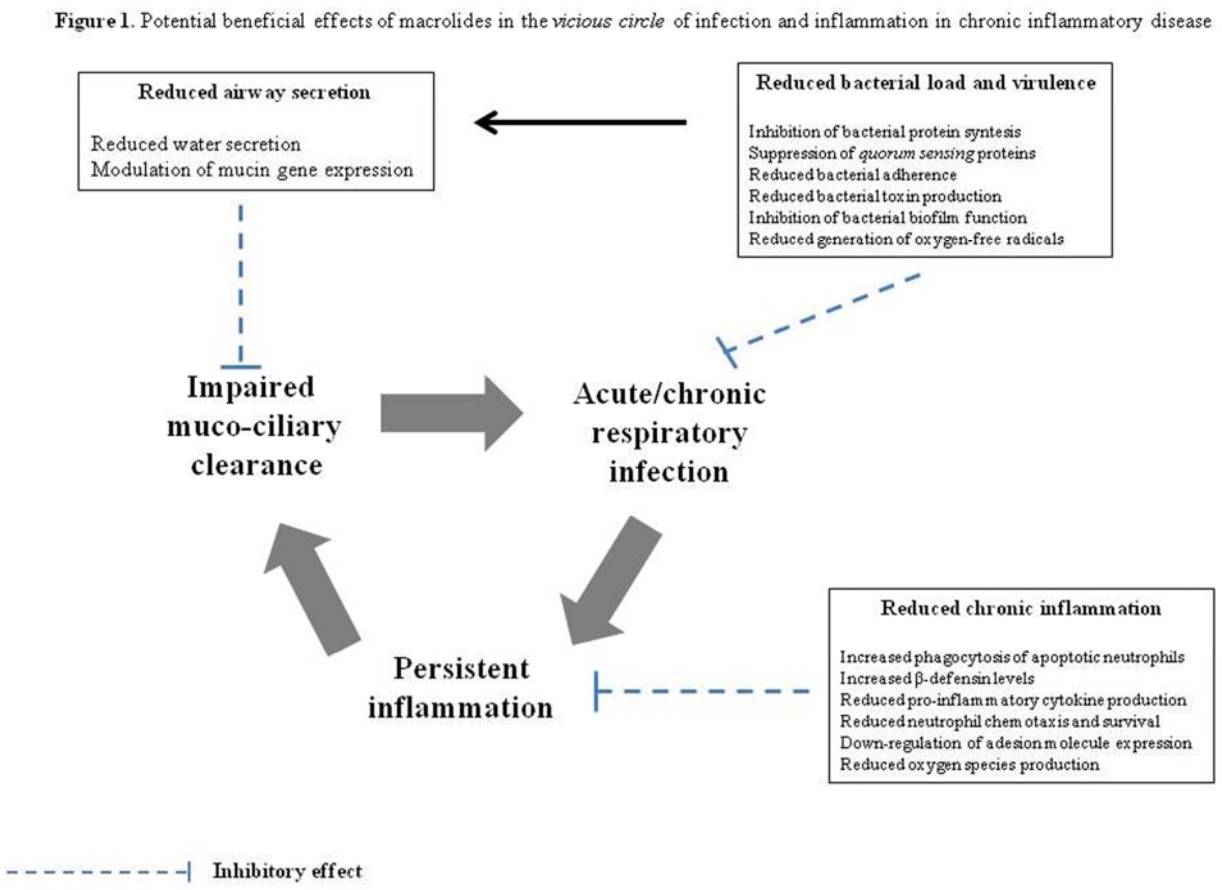

Figure 2. Diffuse panbronchiolitis. High Resolution Computed Tomography section through the right middle and lower lobes showing a profusion of small nodules and branching structures (*tree-in-bud* pattern) with accompanying cylindrical bronchiectasis. Slide courtesy Nicola Sverzellati

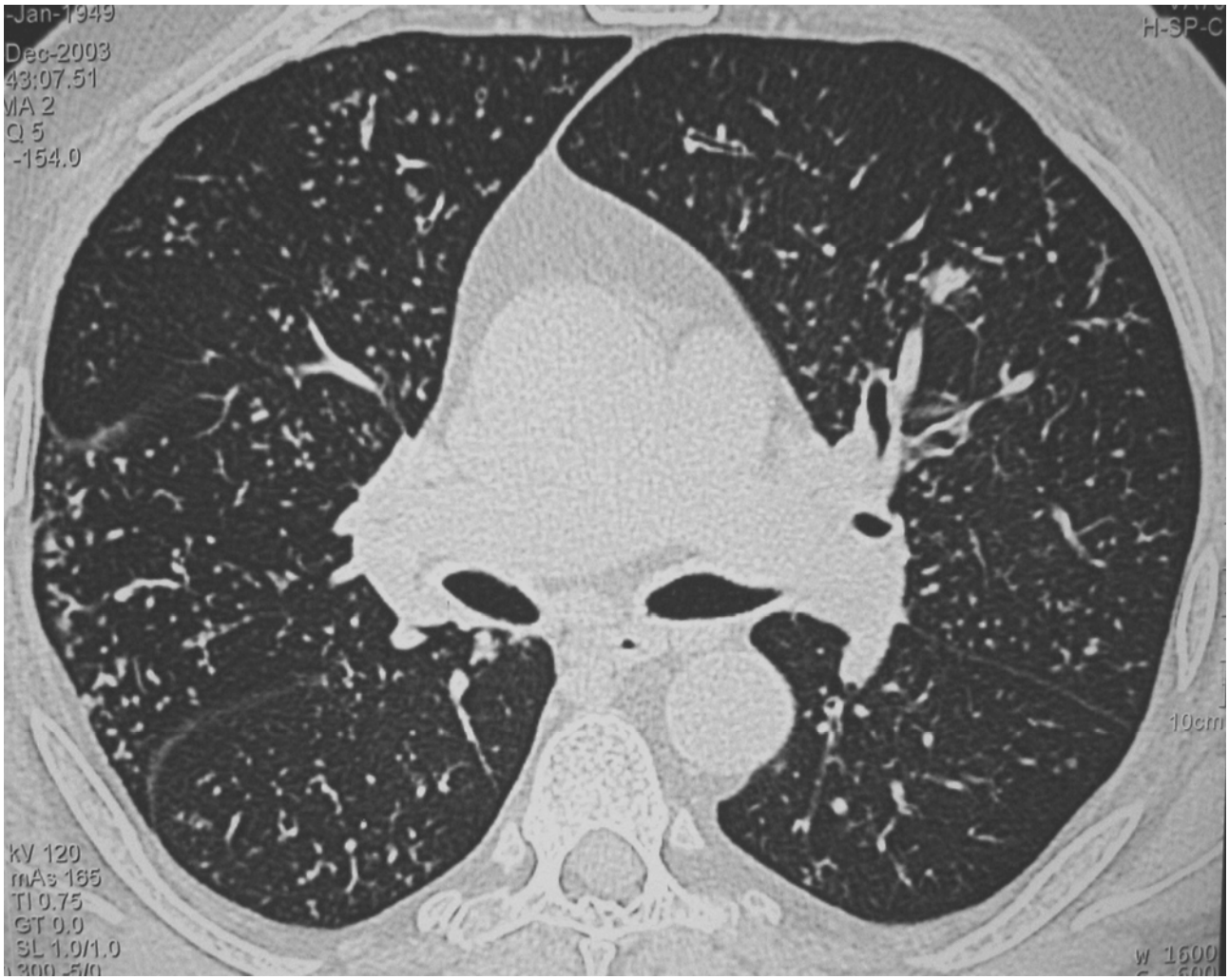

Figure 3. Cystic fibrosis. Upper lobe predominant panlobular bronchiectasis with large mucus plugs in a 14-year-old patient.

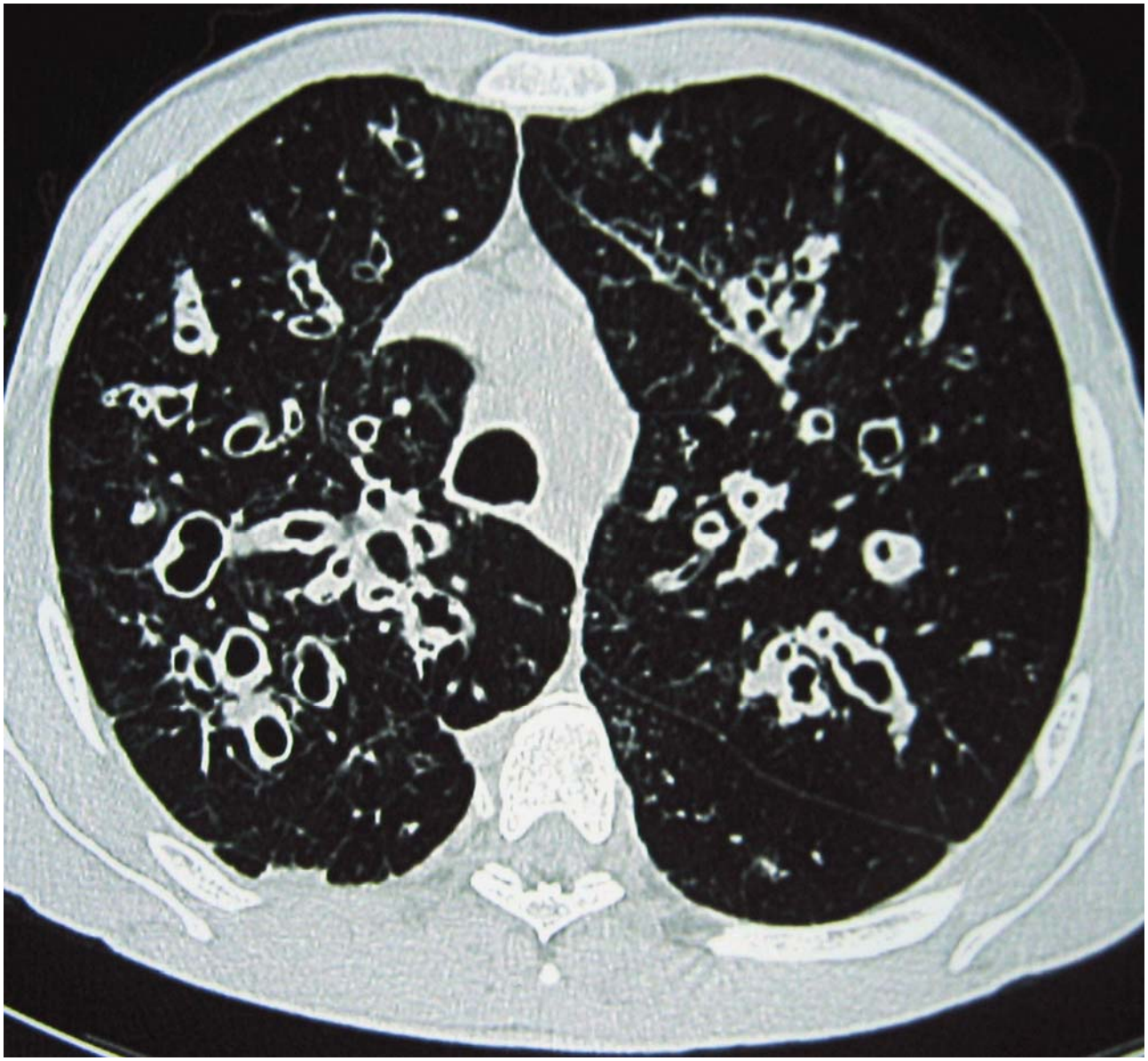

Figure 4. Bronchiectasis in a young patient with asthma complicated by allergic bronchopulmonary aspergillosis. Mucoid impaction and small nodular branching opacities are also present in the right lung.

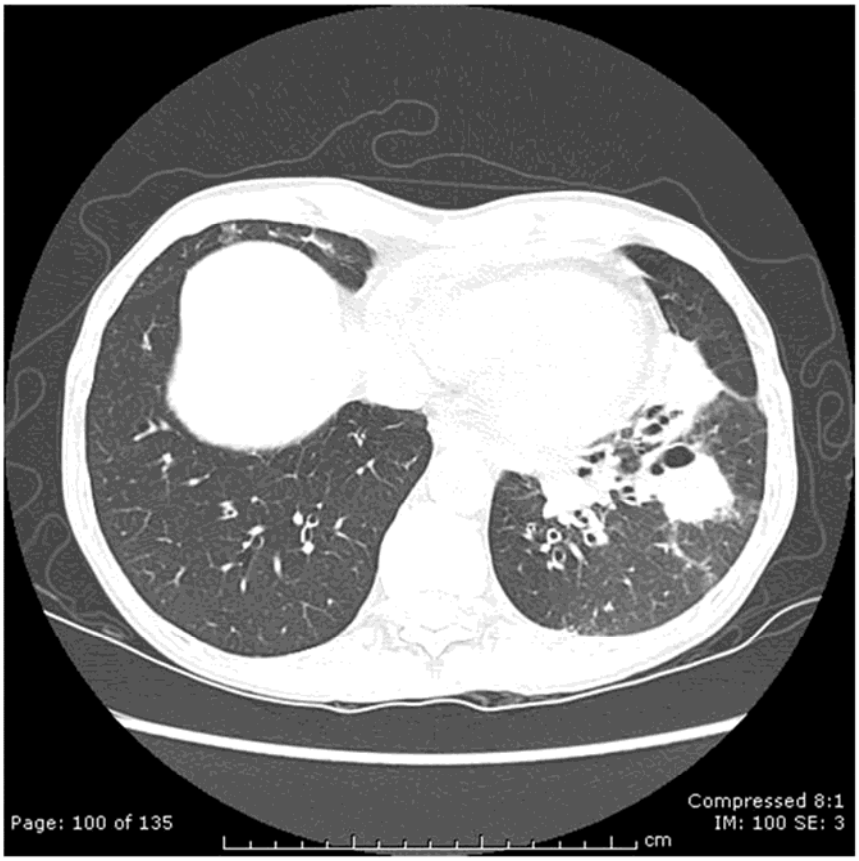

Figure 5. Constrictive bronchiolitis in a patient who has undergone bone marrow transplantation. There is a mosaic attenuation pattern and the calibre of the pulmonary vessels within the areas of decreased attenuation is reduced. Thick-walled and dilated subsegmental bronchi are also present.