Macrolide maintenance treatment for bronchiectasis

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CHAPTER 4

Immunomodulatory effects of macrolide antibiotics – part 2: advantages and disadvantage of macrolide maintenance therapy.

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Abstract

The available evidence for long-term, low-dose treatment with 14- and 15-membered ring macrolides in non-CF bronchiectasis, COPD, chronic sinusitis and asthma is reviewed, with special attention to possible adverse effects and emergence of resistance during long term macrolide treatment.

Macrolide maintenance therapy has been proven to be of benefit in diffuse panbronchiolitis and cystic fibrosis, presumably due to an anti-inflammatory mechanism of action, on top of its direct anti-microbial effect. Solid evidence to justify this treatment regimen non-CF bronchiectasis, asthma or sinusitis is still lacking, although a beneficial effect of long term macrolide therapy has been found in small clinical trials on these subjects. Data from randomised trials of long term macrolide treatment in COPD are conflicting. A sufficiently long duration of treatment and careful selection of patients appears to be crucial. Apart from beneficial effects, possible side effects of macrolide treatment should be taken into account, the most important being gastro-intestinal upset and cardiac arrhythmias. Development of macrolide resistance among respiratory pathogens is very common during long-term macrolide treatment. Whether this finding is clinically significant is a matter of debate.

Introduction

In pulmonary practice, prolonged macrolide therapy with reduced dosages has become increasingly popular for the treatment of patients with chronic inflammatory conditions, such as non-CF bronchiectasis and sinusitis, who have recurrent infections or other signs of ‘badly-regulated disease’. In this article we aim to provide an overview of the available evidence for macrolide maintenance therapy in these chronic inflammatory pulmonary conditions.

The concept of treating inflammatory lung diseases with macrolide maintenance therapy originates from Japan, where, in 1987, Kudoh and colleagues [1] reported a spectacular decrease in symptoms and increase in life expectancy in patients with diffuse panbronchiolitis (DPB) following treatment with the macrolide erythromycin. Until then, DPB had been a rapidly progressive and debilitating inflammatory airway disorder carrying a very poor prognosis. This condition is almost exclusively found in Japan and is pathologically characterized by chronic recurrent bronchiolitis and peribronchiolitis with infiltration of the small airways. This can eventually lead to complete occlusion of the lumen of the respiratory bronchioles, through the formation of lymph follicles, granulomas and scar tissue. Clinically, pulmonary complaints, such as dyspnoea and productive cough are almost always accompanied by features of chronic rhinosinusitis [2,3]. High numbers of neutrophils and lymphocytes, together with high levels of IL-8 and other pro-inflammatory cytokines and chemokines are found in BAL fluid of DPB-patients [4,5]. This indicates a chronic inflammatory process, which is further deteriorated by the presence of pathogenic micro-organisms. In the early course of the disease, sputum cultures of DPB-patients mainly yield Haemophilus influenzae, which is in many cases replaced by Pseudomonas aeruginosa (PA) in a more advanced stage of DPB [4,6].

In addition, there appears to be a genetic component contributing to the disease mechanism. In approximately 60% of DPB patients the human leukocyte antigen (HLA)-B54 haplotype is found, which is only present in 11% of the healthy Japanese population [7].

After the introduction of erythromycin as standard therapy for DPB in 1987, an impressive increase of 10-year survival was reported; 10-20% to more than 90% [2,8-10].

The unexpected success was attributed to a previously unknown anti-inflammatory effect in addition to the anti-microbial potency of erythromycin. This theory is supported by more recent studies, which demonstrated that serum levels of erythromycin in DPB-patients were well below minimal inhibitory concentrations (MIC) for the detected pathogens [9]. Furthermore, Nakamura et al [11] showed that the beneficial effect of macrolides on pulmonary function and general well-being is frequently found without a change in the number or type of bacterial isolates.
Macrolides have been demonstrated to reduce IL-8 and IL-1β levels in BAL-fluid of DPB patients [12]. By influencing the production of these and other cytokines, they have a dampening effect on the pro-inflammatory response. Furthermore, the majority of cells involved in both the innate and adaptive immune-response, are, one way or the other, influenced when macrolide antibiotics are administered. Their anti-bacterial effect consists of inhibition of bacterial protein synthesis, impaired bacterial biofilm synthesis, and attenuation of other bacterial virulence factors. Especially the effect on biofilm formation is suggested to be of importance in DPB-patients who are frequently colonised with biofilm-forming P. aeruginosa. Results of Japanese in vitro studies indicate that azithromycin and clarithromycin change the structure of bacterial biofilms via inhibition of polysaccharide synthesis, a major biofilm component [13,14]. An insufficient biofilm allows for enhanced phagocytosis and clearance of bacteria by alveolar macrophages [15,16].

The effectiveness of macrolide maintenance therapy in order to reduce disease activity, exacerbations and decline in lung function has been well proven in cystic fibrosis (CF) [17]. Since 2002, five large randomised trials, with a total of 608 patients included, have been published in which the role of macrolide maintenance treatment in CF is addressed [18–22]. These studies all used azithromycin in different dosages (250 or 500 mg daily, 250 or 500 mg three times a week, or 1200 mg once a week) with a mean duration of 200 days. All studies showed a significant increase in lung function (FEV1). Additional outcomes were a decrease in the frequency and duration of infectious exacerbations, improvements in physical condition and gain of body weight.

The most recent trial was performed by McCormack et al [22]. In their double-blind randomised study in 208 patients, improvement in lung function, CRP, days spent in hospital, admission rate and nutritional status was demonstrated after 6 months of treatment with azithromycin. Daily (250mg) and weekly (1200mg) administered azithromycin showed similar outcomes, although gastro-intestinal adverse effects where more common with weekly therapy. Nowadays macrolide maintenance therapy is considered common practice in the treatment of CF-patients, especially in those colonised with P. aeruginosa (PA). Colonisation with PA is associated with reduced survival and faster decline in lung function in DPB and CF [4,23,24]. The abovementioned trials also included patients without PA colonisation, but to date no randomised study in CF-patients uninfected with PA had been performed. However, in a recently published article, Saiman et al study the effect of azithromycin (250-500 mg three times weekly, 24 weeks vs. placebo) on pulmonary function in 260 children with CF and mild lung disease [25]. Only patients with negative respiratory tract cultures for PA for at least one year were included. Treatment with azithromycin did not result in improved pulmonary function in this relatively healthy patient group. On the other hand, a promising amelioration in secondary endpoints, weight and frequency of infectious exacerbations, was observed after treatment with azithromycin.

The improvement of pulmonary function, reduction of exacerbation frequency and improvement of quality of life shown in the abovementioned trials is often contributed to an anti-inflammatory effect of macrolide treatment [18,19,22]. Macrolides have a direct anti-microbial effect, but also modulate many aspects of the immune-response. This so-called ‘immune-modulatory effect’ is exclusively demonstrated for 14- and 15-membered ring macrolides (erythromycin, clarithromycin, roxithromycin and azithromycin, respectively) [26-30]. The dual effect on both inflammation and bacterial colonisation appears to make 14- and 15-membered ring macrolides exceptionally suited to contribute to the treatment of chronic inflammatory diseases like COPD and bronchiectasis. The fact is that the key feature of chronic pulmonary diseases like COPD and bronchiectasis and, to a lesser extent, asthma and sinusitis is distortion of the inflammatory response, allowing for bacterial colonisation [31–33]. An overview of the biological mechanisms through which macrolides exert their immunomodulatory effect is provided in part 1 of these series of articles.

Considering the increasing popularity of macrolide maintenance therapy, concern about possible disadvantages seems appropriate. In the past, macrolides, especially erythromycin, where known for their ability to cause cardiac arrhythmias and hearing loss when administered in high dosages [34,35]. Finding out whether the above also applies to long-term low-dose macrolide therapy is relevant to clinical practice. In addition, reduced susceptibility or resistance to macrolides is very likely to develop when these drugs are administered in low dosages during longer periods of time.

We performed a literature search for studies exploring clinical effectiveness of long-term macrolide therapy in COPD, chronic rhinosinusitis, non-CF bronchiectasis and asthma. We focused primarily to include randomised controlled trials, if available. An additional search was performed for studies about macrolide safety and emergence of macrolide resistance during long-term macrolide therapy. As none were found, the search was broadened to macrolide safety and resistance in general, with special attention to ototoxicity and cardiac toxicity.

**Non-CF bronchiectasis and long-term, low-dose macrolide treatment**

In bronchiectasis, irreversible, pathologic dilatation of the small and medium-sized bronchi results from an ongoing cycle of chronic inflammation and bacterial colonisation (vicious circle theory) [31,36,37]. Although the etiology remains unclear in a large percentage of patients (53-60%), common causes include immune defects, early childhood infections, and aspiration [38-40]. Clinically, this results in chronic and sometimes debilitating symptoms of productive cough, dyspnea and recurrent infections. As early as 1965, maintenance therapy with macrolide antibiotics (e.g. oleandomycin) was investigated as a potential remedy for
chronic symptoms in patients with hypogammaglobulinemia and bronchiectasis [41].

Three small, randomised controlled trials investigating the efficacy of macrolide antibiotics in non-CF bronchiectasis were published in the last decade. Patient numbers did not exceed thirty-five and all trials used different macrolide products, administered for relatively short periods of time. A total of 59 children and 21 adults with proven bronchiectasis were treated with roxithromycin (4 mg/kg b.i.d. for 12 weeks), erythromycin (500 mg b.i.d. for 8 weeks) or clarithromycin (15 mg/kg daily for 12 weeks). Improvement of sputum properties, a decrease in markers of airway inflammation, reduced sputum volume and decreased bronchial reactivity as measured by methacholine challenge were demonstrated in patients receiving macrolide treatment as compared to controls [42-44]. Only one randomised trial demonstrated a small but significant improvement in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) [43]. A small open-label, crossover study, enrolling 12 patients, investigated the effect of azithromycin (500 mg two times a week) added to standard treatment during 6 months [45]. Despite the small numbers, this study showed significantly fewer infectious exacerbations and reduced sputum volume. No change in lung function measurements was found. A fairly recently performed patient-control study showed comparable results concerning exacerbation frequency. Long-term azithromycin treatment (250 mg three times a week for 4-38 months) of thirty-nine patients with bronchiectasis and frequent exacerbations (> 4 in the past 12 months) resulted in a significant reduction in infectious exacerbations. Furthermore, these patients reported a significant improvement of symptoms. An improvement of all lung function parameters was reported, but only the improvement in carbon monoxide transfer factor (TLCO) reached statistical significance. The severity of symptoms in this group of patients made the researchers abstain from a placebo-controlled study design [46].

In conclusion; data from numerous, but mainly small studies suggest that long-term macrolide treatment in patients with non-CF bronchiectasis could have a positive influence on frequency of infections, sputum volume and inflammation. The effect of macrolide maintenance therapy on lung function remains uncertain. In turn, improvement of these parameters has a potentially large effect on quality of life in this group of patients.

**COPD and long-term, low-dose macrolide treatment**

Most research on the role of macrolide antibiotics in COPD focuses on short treatment in acute exacerbations. Current guidelines promote the administration of a short course of antibiotics to patients with an AECOPD and increase in sputum purulence or signs of pneumonia [47]. A meta-analysis of macrolide antibiotics vs. quinolones and macrolides vs amoxicilline/clavulanate in patients with acute bacterial exacerbations of chronic bronchitis showed no difference in treatment success [48].

Based on the most recent Cochrane review, long-term, prophylactic antibiotic therapy in stable COPD is not recommended [49]. The reviewers, however, mainly included trials conducted over 30 years ago, when antibiotic susceptibility and availability may have been different. Moreover, they did not distinguish between macrolide and other groups of antibiotics.

Only two randomised trials investigate the efficacy of long-term macrolide treatment in COPD. Banerjee et al [50] investigated 67 patients in a prospective double-blind randomised placebo-controlled study using clarithromycin 500 mg during 3 months. Although a large number of different parameters were measured (health status, quantitative sputum cultures, exacerbation rate, spirometry, CRP, shuttle walk test), no significant change was seen in any of them. The authors state that this may be due to the studies’ small number of included patients and the relatively short treatment time. Results of another very recent study seem to support their statement. Seemungal et al [33] established a positive effect of prophylactic macrolide treatment in moderate to severe COPD in their study with a longer treatment time and longer follow-up. In this single centre, randomised, double-blind, placebo-controlled trial they treated 109 patients with erythromycin 250 mg BD or placebo during one year. Their most important finding was a 35% reduction of exacerbations in the macrolide arm of the study compared to the placebo arm, with a tendency towards shorter and less severe exacerbations in the macrolide arm. No significant change was found in lung function parameters, sputum and airway inflammatory markers, side-effects and bacteria isolated.

Contemplating these results and the evidence of the anti-inflammatory and antibacterial effect of macrolide antibiotics, one could argue that low-dose macrolides, when applied long enough, may have beneficial effects in moderate to severe COPD. Currently, a large multicenter study is performed, investigating the effect of chronic macrolide administration on the frequency and severity of COPD exacerbations. 1130 patients receive azithromycin (250 mg once daily) or placebo in a randomized, double blind fashion[51,52]. Results of this study will presumably provide more insight into the role of macrolide prophylaxis in COPD.

**Long-term, low-dose macrolides in chronic rhinosinusitis**

Chronic rhinosinusitis is characterized by hyperplasia, hypertrophy and hypersecretion of the of the nasal and paranasal sinus mucosa. Typically, high levels of neutrophils and pro-inflammatory cytokines, especially IL-8, are found in nasal secretions. In ear, nose and throat- medicine, there appears to exist a moderate recommendation for the use of long-term macrolide treatment in chronic sinusitis [53]. This recommendation however, is
Based on limited data. Most studies that focus on long-term macrolide treatment in chronic sinusitis are small, open-label series. Consistent findings across these studies have been improvement in sinusitis symptoms, shrinkage in the size of nasal polyps and a decrease in levels of pro-inflammatory cytokines in nasal secretions [54-58]. In 2006, the first double-blind randomised, controlled trial (roxithromycin 150 mg OD or placebo for three months) was published [59]. The macrolide-treated group (n=29) showed a significant improvement in symptom scores, endoscopy findings and olfactory function. Nasal lavage essays showed decreased levels of IL-8 in the roxithromycin-treated group. Significant improvements started to occur after 6 weeks of treatment. These findings are consistent with previous open-label studies that showed that a prolonged course of macrolide therapy of minimal 12 weeks is required in order to reach and maintain maximal clinical benefit [54,60]. A subgroup analysis showed that the improvement of symptoms was most distinct in patients with low levels of IgE. This phenomenon was also observed in an earlier Japanese open-label study. Out of 16 patients receiving macrolide maintenance therapy, the ones with low levels of IgE (below 250U/ml) showed a significantly higher rate of symptomatic improvement [61]. These findings suggest that long-term macrolide treatment could be beneficial in chronic rhinosinusitis, but treatment periods longer than 12 weeks are necessary to maintain the beneficial effect. Furthermore, a subgroup of patients with low levels of serum IgE can be identified that seems to have most benefit most of macrolide treatment.

### Long-term, low-dose macrolides in asthma

Bronchial hyperresponsiveness in asthma is related to airway inflammation. Asthma is considered a chronic inflammatory disease of the airways which in most cases requires long-term anti-inflammatory therapy [32,62]. Chronic inflammation in asthma is characterized by increased numbers of activated lymphocytes, eosinophils and variably reported increases of mast cells. The walls of the conducting airways are thickened, the lumen obscured with an infiltrate of inflammatory cells and excess mucus [63]. Published reports have demonstrated an anti-inflammatory effect of macrolide antibiotics in asthma. This class of antibiotics has been found to reduce airway hyperresponsiveness, NO-production, cytokine expression and eosinophilic infiltration [64-69]. Another mechanism of action is proposed by Takizawa et al [70]; they demonstrated an attenuation of endothelin-1 (a potent bronchoconstrictive peptide) expression by bronchial epithelial cells after in vitro treatment with erythromycin and clarithromycin.

Two ways of long-term application of macrolide antibiotics in asthma have been specifically studied.

1. **Addition of troleandomycin to steroid treatment:** Troleandomycin (TAO), a 14-membered ring macrolide, was first described as a treatment for steroid dependent asthma in 1974 [71]. Besides its anti-bacterial properties, anti-inflammatory effects of TAO have been reported. However, its most important mechanism of action in steroid dependent asthma patients appears to be the increase of bioavailability of steroids. Use of TAO slows the elimination of methylprednisolone, effectively doubling the half life, due to reduced liver metabolism [72-74]. Initial research in small groups of patients showed promising results. 16 severe, corticosteroid-dependent yet resistant outpatient asthmatics were well controlled after 4 months of addition of TAO with minimal side effects [75]. Wald et al [76] introduced another protocol with a lower starting dose of TAO and rapid steroid tapering. Side effects were even less present and a marked increase in pulmonary function parameters was observed. Nevertheless, as time went on, increasing concern arose about increase in corticosteroid induced side-effects in patients receiving TAO and steroids [77]. Since 1990, three randomised trials investigating the use of TAO in patients with corticosteroid-dependent asthma have been published [78-80]. Two of these reported more steroid-related side-effects in the patients who were treated with TAO in addition to corticosteroids [79,80]. A meta-analysis of 108 patients (75 adults and 33 children) in these three studies failed to show a significant reduction in the required dose of oral steroids in patients treated with TAO. Furthermore, there was no improvement in lung function when pooled data from two of these studies were analyzed [81].

A steroid sparing effect of clarithromycin was demonstrated in a small study in three steroid-dependent asthma patients by Garey et al [82]. They noticed a significant decrease in prednisone requirements in all three patients and discontinuation of prednisone treatment in two patients due to clarithromycin treatment.

2. **Treatment of bacterial infection:** *Mycoplasma pneumoniae* (MP) or *Chlamydia pneumoniae* (CP) may be involved in asthma pathogenesis [83]. In 2001, the first systematic evaluation of CP and MP infection in 55 patients with stable asthma, showed the presence of either MP or CP as detected by PCR in 56.4%, as compared to 9% in healthy control subjects (p<0.02) [84]. The authors concluded that a significant number of patients with stable asthma are infected by one of these micro-organisms. Furthermore, a substantial number of acute exacerbations (18-21%) in asthma is caused by MP [85-87]. The presence of such micro organisms predisposes for more severe asthma and more frequent and serious exacerbations [88-90]. Certain features of asthma, such as bronchial hyperactivity and impaired pulmonary function have been proven to persist long after *chlamydial or mycoplasmal* infections [91,92].
These findings formed the starting point of the randomised trials that investigated the role of macrolide treatment in subjects with serological evidence of infection with either MP or CP.

Kraft et al [93] treated 55 asthma patients with either clarithromycin (500 mg bid) or placebo. When subjects who received clarithromycin were divided by PCR status, only patients with positive PCR findings for CP or MP showed a significant increase in FEV1 and reduced expression of IL-5 (a pro-inflammatory cytokine). No improvement of any parameter was seen in PCR-negative, clarithromycin-treated patients. In a large multi-center trial, 232 subjects with asthma and high titers of IgA and/or IgG antibodies to C. pneumoniae were randomised to roxithromycin 150 mg bid or placebo for 6 weeks [94]. Treatment with roxithromycin lead to minimal improvement in asthma control (slight improvement in morning PEF). Due to this small effect, the calculated sample size was found to be insufficient to gain adequate power. They found no change in symptom scores and improvement in peak flow measurement disappeared after treatment was discontinued. Hahn et al [95] completed a community based pilot study in which 45 patients with mild to moderate asthma were randomised to azithromycin (600 mg weekly) or placebo for 6 weeks in addition to their usual asthma care. Not only did they find a clear correlation between asthma severity and serum IgA antibodies against CP, they also demonstrated a beneficial effect of azithromycin on overall asthma symptoms. Due to its pilot nature and the small number of participants, no significant conclusions could be drawn.

Although there is convincing evidence for a role of MP and CP in the pathogenesis of asthma, results of randomised trials investigating the effect of macrolide therapy in asthmatic patients with serologic evidence of atypical infection, are, to date, unsatisfactory. Perhaps advanced techniques using qPCR might elucidate the role of bacterial burden and potential benefit of long-term macrolide treatment in asthmatic patients with significant bacterial burdens.

The use of macrolide maintenance therapy in asthma in general has been subject of a Cochrane review in 2005 [96]. After long-term macrolide treatment no significant change in lung function and only a small symptom reduction was found, although serum markers of eosinophilic inflammation were found to be markedly decreased.

The authors concluded: ‘Even though some clinical data indicate a positive effect of macrolides in asthmatic patients in the absence of relevant side effects, these data are insufficient to recommend the routine use of macrolides for control of asthma at present.’

Randomised controlled trials performed after 2005 focus on the possible immune-modulating effect of macrolides in asthma. A small Italian study investigated the effect of 8 weeks azithromycin treatment vs. placebo in 16 asthmatic children [97]. Although they found a significant decrease in inflammatory markers in the azithromycin treated group, no change in lung function was observed. Simpson et al [98] distinguished two types of asthmatic patients; allergic asthma, characterized by eosinophilic inflammation and high IgE-titers, as opposed to non-eosinophilic asthma (NEA) which features increased neutrophil numbers and high IL-8 levels in the airways. Forty-six patients with refractory asthma, randomised to clarithromycin (500 mg bid) or placebo, were stratified according to neutrophil proportion and treated for 8 weeks. The authors demonstrated a significant reduction in IL-8 and neutrophil numbers and an improvement of QOL in all patients after 8 weeks of clarithromycin treatment. In view of the fact that they found a non-significant fall in all other inflammation markers, the authors suggest that clarithromycin causes an overall down-regulation of neutrophil activation and mediator release. The anti-inflammatory effect was most marked in NEA patients (with high neutrophil proportions), suggesting that long-term macrolide therapy could prove a good add-on therapy in refractory NEA.

So, in line with the previously mentioned studies on chronic rhinosinusitis, it is plausible that a subgroup of patients with high IL-8 and low IgE-levels, benefits most from long-term macrolide treatment.

**Long-term macrolide therapy in cryptogenic organizing pneumonia**

Organizing pneumonia is a non-specific inflammatory disorder, pathologically characterized by the presence of granulation tissue and fibrosis in the alveoli and distal bronchioles [99]. In the presence of specific clinicoradiological features, this entity is defined as cryptogenic organizing pneumonia (COP).

In 1993, Japanese researchers demonstrated that some patients with COP show clinical and radiological improvement after prolonged treatment with erythromycin [100].

A more recent report on clarithromycin treatment in three patients with COP, describes complete resolution of pulmonary and systemic symptoms in two of them, while being treated with low dosages (250 mg once or twice daily) for three months [101]. A possible mechanism of action is proposed by Hotta et al [102]. They demonstrated a significant decrease of IL-8 levels and neutrophil numbers in BAL-fluid of 8 patients with COP after treatment with erythromycin (600mg daily for three months), indicating that macrolides cause inhibition of neutrophil accumulation in the peripheral airways in patients with COP.

No large-scale studies however, are available to confirm these findings. Up to now corticosteroids are advised as first choice for the treatment of COP.
Safety of long-term macrolide treatment

Gastro-intestinal complaints are the most common adverse effects in patients receiving macrolide therapy. Gastro-intestinal adverse effect rates of 15-20% for erythromycin, 8.7% for clarithromycin and 9.6% for azithromycin have been observed in patients receiving short courses of macrolides [103]. In randomised trials of long term, low dose macrolide treatment in chronic pulmonary diseases, mild to moderate gastro-intestinal complaints are reported, which hardly ever cause study drug discontinuation (table 1).

Table 1: Adverse events reported in randomised trials of long term macrolide treatment in chronic sinus-pulmonary diseases. * (no of patients), **no significant difference between study drug and placebo

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No of patients</th>
<th>Intervention</th>
<th>Adverse events in treatment group*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolter 2002 [10]</td>
<td>CF, adults</td>
<td>60 azithromycin 250mg/day; 3 months</td>
<td>urticaria (1), rash (1)</td>
</tr>
<tr>
<td>Equi 2002 [8]</td>
<td>CF, children</td>
<td>41 azithromycin 250 or 500mg/day; 6 months</td>
<td>transient elevation of liver enzymes (1)</td>
</tr>
<tr>
<td>Clement 2006 [7]</td>
<td>CF, children</td>
<td>82 azithromycin 250 or 500mg, 3x/wk; 12 months</td>
<td>gastrointestinal (16), ENT-infections (14), headache (2)**</td>
</tr>
<tr>
<td>McCormack 2007 [11]</td>
<td>CF, adults + children</td>
<td>208 azithromycin 250mg/day vs. azithromycin 1200mg/wk; 6 months</td>
<td>&gt;4x increase in liver enzymes (8), gastrointestinal (36)</td>
</tr>
<tr>
<td>Steinkamp 2008 [82]</td>
<td>CF, adults + children</td>
<td>38 azithromycin 500/750/1000/1250 mg/wk; 8 weeks</td>
<td>gastrointestinal, rash</td>
</tr>
<tr>
<td>Black 2001 [77]</td>
<td>Asthma, adults</td>
<td>232 roxithromycin 150mg bid; 6 weeks</td>
<td>gastrointestinal (19), transient elevation of liver enzymes (6)</td>
</tr>
<tr>
<td>Kostadima 2004 [83]</td>
<td>Asthma, adults</td>
<td>63 clarithromycin 250mg bid / tid; 8 weeks</td>
<td>withdrawal due to gastro-intestinal side effects (1)</td>
</tr>
<tr>
<td>Hahn 2006 [78]</td>
<td>Asthma, adults</td>
<td>45 azithromycin 600mg/week, 3 months</td>
<td>mild to moderate gastro-intestinal side effects (5)</td>
</tr>
<tr>
<td>Wallwork 2006 [43]</td>
<td>Chronic sinusitis, adults</td>
<td>64 roxithromycin 150mg/day; 3 months</td>
<td>withdrawal due to gastro-intestinal side effects (1)</td>
</tr>
<tr>
<td>Banerjee 2008 [36]</td>
<td>COPD, adults</td>
<td>46 clarithromycin 500mg/day; 3 months</td>
<td>withdrawal due to gastro-intestinal side effects (1)</td>
</tr>
<tr>
<td>Seemungal 2008 [19]</td>
<td>COPD, adults</td>
<td>109 erythromycin 250mg bid; 12 months</td>
<td>gastrointestinal (8), rash (3), tinnitus (1)**</td>
</tr>
</tbody>
</table>

Other infrequently reported side effects related to macrolide use are rash (0.5 – 6%) and hepatotoxicity (most frequently a transient increase in liver enzymes or cholestasis) [103,104]. As all macrolide-related side effects, these are more common following treatment with erythromycin than with the other 14- and 15-membered ring macrolides [103,105]. Furthermore, the incidence of adverse effects increases when macrolides are administered in larger dosages or reaching higher serum levels [22,103,106].

Ototoxicity and cardiac toxicity are familiar, though very rare, side effects of macrolide antibiotics. Because of their infrequent occurrence, these side effects are hardly ever observed in clinical trials. Few of the abovementioned trials monitored for cardiac arrhythmia or hearing loss, so no solid data are available concerning the incidence of these side effects during long term use of macrolides. The incidence and outcome of these conditions during short term use of macrolides has, however, been established. Furthermore, the potential seriousness of these two side effects makes them fit to be discussed in detail.

Ototoxicity:

Ototoxicity caused by macrolide use is typically described as reversible sensorineural bilateral hearing loss, involving the lower or speech frequencies. Most articles about this subject are case reports or review articles, mainly published more than 15 years ago [103,107-109]. Swanson et al [109] conducted the only prospective case-control study to date, in which hearing tests were carried out in 45 patients receiving intravenous antibiotic treatment for pneumonia. 21% of patients who were treated with high dosages of erythromycin developed varying degrees of hearing impairment, as opposed to none of the patients who were treated an other anti-microbial agent. They furthermore demonstrated that only renal impairment or decreased total systemic clearance was associated with the development of hearing loss in this small group of patients.

This study and other reports point out, that macrolide use causes ototoxicity in an obviously dose-dependent fashion. Only daily macrolide dosages similar to azithromycin 1500 mg or clarithromycin 2000 mg changed the cochlear response rate in guinea pigs [110]. Case reports about erythromycin ototoxicity describe hearing impairment mainly in association with intravenous therapy and/or dosages > 4000 mg od [104,107,108,111].

Ototoxicity following long term application of macrolide antibiotics has been described in the treatment of Mycobacterium ovium complex infections. In a prospective, non-blinded study, 25% of patients receiving high dosages of azithromycin (600 mg daily) complained of hearing impairment. This was confirmed by audiometry in 6 out of 10 patients. After decreasing the dosage of azithromycin to 300 mg/day or lower ototoxicity was no longer noticed, which was confirmed by audiological testing in 3 of these patients [106]. Wallace et al [35] also report reversible hearing loss in their series of patients with AIDS.
and disseminated *M. avium* disease. 14 out of 21 patients who were treated with daily dosages of 500 mg azithromycin as part of a 3-drug combination regimen between 1992 and 1993, spontaneously complained of hearing loss. No more hearing loss occurred after replacement of azithromycin for clarithromycin in their standard treatment regimen. A few years later, Tseng et al [112] reported reversible ototoxicity in 17% of 46 HIV-patients treated with azithromycin 600mg daily.

No solid information is available concerning the incidence of ototoxicity during long-term macrolide use in lower dosages.

In conclusion, macrolide antibiotics are able to cause hearing loss that is almost always reversible and apparently only when administered in high dosages. The incidence of ototoxicity during low-dose long-term macrolide use is unknown, but, considering the above, probably negligible.

### Cardiac toxicity

In case reports, macrolide antibiotics have been associated with prolongation of the QT-interval and torsades de pointes (TdP). The European Society of cardiology considers erythromycin (EM) and clarithromycin as drugs that are particularly associated with cardiac arrhythmias [113]. Intravenous use of erythromycin has been associated with a particular high risk of arrhythmias, probably due to the poorer absorption of oral preparations [113,114]. One large cohort study in 2004 found a twofold increased risk of sudden death from cardiac causes among patients currently using erythromycin, compared to those who had not used any of the antibiotic medications studied [34]. TdP is a polymorphic ventricular tachycardia, usually preceded by prolongation of the QT-interval, caused by altered cardiac repolarisation. It may be asymptomatic but has also been associated with syncope and sudden death. Drug induced prolongation of the QT-interval is generally regarded as a reliable predictive measure for the risk of TdP arrhythmias.

Macrolides have two potential effects on the QT-interval: 1. Intrinsic prolongation: macrolide antibiotics prolong the repolarisation period of the action potential by blocking the HERG potassium channels [115]. 2. Inhibition of metabolism of other pro-arrhythmogenic drugs by acting on cytochrome P450 in the liver. When, for instance, erythromycin and other inhibitors of cytochrome P450 are concurrently prescribed, a 5-fold greater risk of cardiac sudden death was reported [34]. Patient characteristics, associated with a greater risk of developing cardiac arrhythmias following macrolide use are shown in table 2 [114,116,117].

Information about the incidence of (fatal) cardiac arrhythmias associated with macrolide use most often comes from cohort studies and adverse events reporting systems. The only randomised clinical trial of long term macrolide treatment including follow-up ECGs reported no arrhythmias [50].

Retrospective evaluation of reports regarding TdP or ventricular tachycardia related to macrolides (erythromycin, clarithromycin and azithromycin) in the US Food and Drug Administration Adverse Events Reporting System (FDA-AERS) yielded 156 reports in a 13-year period of time (1987-2000). In half of these cases (n=78), a macrolide with no concomitant use of other QT-prolonging drugs was involved. Fatal outcomes were mentioned in 12% (n=9) of macrolide-only reports. Limitations of this analysis brought forth by the authors were the well known biases of spontaneous reports and the fact that TdP was not electrocardiographically confirmed in all cases [117]. Incidence of spontaneous reports of TdP marked out against the number of macrolide prescriptions from 1993-2000 is 0.06 (azithromycin) - 0.18 (clarithromycin) per million prescriptions, according to FDA databases [http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_02_shaffer_rev/sld020.htm].

The aforementioned data indicate that, although cardiac toxicity is rare, special care must be taken when administering macrolide antibiotics, especially erythromycin IV, to certain groups of patients. In female patients older than 80 years, with cardiac co-morbidity or using other pro-arrhythmogenic drugs, ECG follow-up to observe possible QT-prolongation during use of macrolide antibiotics should be considered.

<table>
<thead>
<tr>
<th>Table 2. Risk factors for QT-prolongation or torsade de points during use of macrolide antibiotics</th>
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<tbody>
<tr>
<td>• Age &gt; 80 years</td>
</tr>
<tr>
<td>• Female gender</td>
</tr>
<tr>
<td>• Heart disease</td>
</tr>
<tr>
<td>• Use of other QT-prolonging medication</td>
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<tr>
<td>• Reduced drug elimination</td>
</tr>
<tr>
<td>• Hypokalaemia / Hypomagnesaemia</td>
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<tr>
<td>• Prolonged QT-interval before therapy</td>
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<td>• Bradycardia</td>
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<td>• Genetic predisposition</td>
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</tbody>
</table>
Macrolide resistance

Epidemiology

Reduced susceptibility to antibiotics of respiratory pathogens can be considered an increasing global problem. In general, macrolide resistance has increased considerably over the last decade [118-121]. Both macrolide resistance rates and resistance mechanisms, however, vary considerably depending on location. The highest incidence of macrolide resistance in *S. pneumoniae* is found in Japan, where 80-100% of pneumococci have been found to be macrolide resistant [118,122]. In contrast, resistance rates in Scandinavia (Norway, Sweden) are remarkably low, about 8-9% [123]. A significant association between prescribing of macrolides and local resistance is observed in most studies [120,123-126].

Together with an increase of macrolide resistance in respiratory pathogens, a parallel increase in oropharyngeal carriage of macrolide resistant commensals is observed. High percentages of macrolide resistance up to 94% among viridians group streptococci are reported in healthy volunteers worldwide [127,128]. Although these commensals usually do not cause infections in healthy persons, they may be considered a threat for two reasons; they could cause infection in immune compromised hosts and they might transfer the resistance determinants to pathogenic streptococci [128,129].

Development of macrolide resistance during long term macrolide therapy

In long-term use of antibiotics, reduced susceptibility of potentially pathogenic microorganisms poses a threat. Nevertheless only a few of the randomised clinical trials mentioned in this review address this problem. The ones that did monitor for resistance found no macrolide resistant organisms during follow-up after three months of macrolide maintenance therapy in COPD (n=46), and chronic rhinosinusitis (n=64) [50,59]. A recently performed trial of erythromycin in COPD (n=109) found no influence on the microbiological profile of sputum by the use of erythromycin. Only one case of erythromycin resistance occurred in the macrolide arm of the study after 12 months [33].

In the field of CF research, where long-term macrolide therapy is often practiced, the problem of reduced susceptibility of micro-organisms following this treatment has been covered more thoroughly, though retrospectively [130]. Phaff et al [131] investigated macrolide resistance of *S. aureus* and *H. influenzae* in sputum isolates of 156 CF-patients receiving azithromycin maintenance therapy with a mean duration of 397 days. Erythromycin resistance in *S. aureus* increased from 6.9% at the commencement of study to 53.8% after 5 years of follow up. Concomitantly a tenfold increase in clarithromycin resistance in *H. influenzae* isolates (3.7 to 37.0%) was observed. Other notable results came from a retrospective study by Tramper-Stranders et al [132]. They noticed macrolide resistance in all (100%) *S. aureus* isolates obtained from 100 CF patients after azithromycin treatment with a mean duration of 3.5 years. Emergence of macrolide-resistant *S. aureus* was not related to pulmonary function decline. Similar numbers were published concerning emergence of macrolide resistant *S. pneumoniae* following macrolide treatment. After 4 years of erythromycin or clarithromycin maintenance treatment, 98.2% of pneumococcal isolates recovered from 57 CF patients showed macrolide resistance [133].

Based on these results, we conclude that macrolide resistance in respiratory pathogens only significantly increases when maintenance therapy is given for a long period of time (3-5 years). Ultimately resistance rates can become very high, up to 100%. A maintenance regimen that involves seasonal administration of macrolides (during the autumn and winter periods), as has already been used in some Dutch hospitals, might attenuate the emergence of resistance. Investigating the effect of such a regimen in a randomised trial might be helpful.

The impact of macrolide resistance on clinical outcome is almost exclusively described in observational studies in patients with community acquired pneumonia (CAP), the results of which are subject to dual interpretation. Although considerable numbers of macrolide-resistant organisms were found, no significantly increased morbidity and mortality was demonstrated in these patients [134-136]. Other authors however, believe that the observational study results indicate that macrolide non-susceptibility is responsible for treatment failure in these patients and may be considered a serious hazard [119,129,137-139].

Macrolide resistance in patients treated for *Mycobacterium avium* complex diseases

Long term macrolide therapy plays a key role in treatment regimens and prophylaxis for *Mycobacterium avium* complex (MAC) and other atypical mycobacteria. According to the guidelines of the American Thoracic Society published in 2007, the standard treatment regimen of MAC pulmonary disease in HIV-negative patients should contain either clarithromycin (500-1000 thrice weekly) or azithromycin 250-600 mg thrice weekly). The dosages depend on the status and/or severity of the disease [140].

Macrolide resistance is much more common in patients receiving macrolide monotherapy or macrolide plus a quinolone for more than one month during their treatment period. Griffith and colleagues [141] report the occurrence of macrolide resistant pathogens in 20% of patients who are initially treated with macrolide monotherapy for MAC lung disease. Conversely, only 4 – 6.6 % of patients with MAC lung disease become resistant when a three-dose regimen, including ethambutol and rifampin or rifabutin, is used from the start of treatment [142,143].
Macrolide resistance in MAC pulmonary disease appears to be associated with higher relapse rates and a poor prognosis. In a retrospective study in 51 patients with MAC lung disease, 1-year mortality increased from 0% to 34%, when patients remained culture positive despite adequate treatment [141]. A randomized study by Benson and coworkers [144] in patients with disseminated MAC showed a spectacular decrease in relapse rates when a three-drug regimen was used (6%), compared to macrolide monotherapy (24%).

To avoid the emergence of resistant organisms, it is recommended that MAC lung disease be treated with a macrolide in combination with two or three other medications [140,145,146].

Conclusion

In pulmonary practice, long-term macrolide maintenance therapy has become increasingly popular for the treatment of patients with other chronic inflammatory conditions, such as COPD, asthma, bronchiectasis and sinusitis, who have recurrent infections or other signs of ‘badly-regulated disease’. Scientific evidence to justify this, however, is still conflicting in the case of COPD and lacking in non-CF bronchiectasis, sinusitis and asthma. Study results to date, show a beneficial effect of macrolides on exacerbation frequency, sputum volume, and inflammatory markers. Low dose macrolides should be applied for at least three months to establish and maintain these advantageous effects. Gastro-intestinal complaints are the most frequently reported adverse effects of long-term macrolide treatment. Increased macrolide resistance among different pathogens has been documented in maintenance treatment, but the clinical significance of this reduced susceptibility to macrolides remains unknown.

Reference list


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