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Neomacrolides in the treatment of patients with severe asthma and/or bronchiectasis: a retrospective observational study

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Abstract:

Rationale: Previous studies have demonstrated that long-term low-dose macrolides are efficacious in cystic fibrosis (CF) and diffuse panbronchiolitis, two chronic neutrophilic airway diseases.

Aims: The aims of this study were to evaluate the efficacy and safety of low-dose neomacrolides as add-on therapy in patients with severe asthma and/or bronchiectasis and to identify predictors for therapeutic response.

Methods: In a retrospective observational cohort study, we examined 131 adult, non-CF patients with severe asthma and/or bronchiectasis, receiving low-dose neomacrolides as add-on treatment. Pulmonary function tests and symptom scores were assessed at baseline and after 3 to 8 weeks of therapy.

Results: After 3–8 weeks of treatment with low-dose neomacrolides, 108 patients were available for evaluation. In asthma patients ($n = 47$), pulmonary function tests and symptom scores improved significantly. Responders ($\geq 7\%$ forced expiratory volume in one second predicted [FEV₁%] improvement) were older (55 vs. 47 years; $p = 0.042$) and had a longer duration of asthma (29 vs. 9 years; $p = 0.052$). In patients with bronchiectasis only ($n = 61$), symptom scores improved significantly. Responders ($\geq 60\%$ symptom score improvement) were older (61 vs. 53 years; $p = 0.004$), more frequently male (53% vs. 27%; $p = 0.043$), and there was a nonsignificant trend towards higher high-resolution CT (HRCT) score for bronchiectasis in responders (6.4 vs. 4.6; $p = 0.053$). In multivariate logistic regression analysis, age and male gender were independent predictors for improvement in this group.

Conclusion: The results of this retrospective study suggest that neomacrolides may be useful as an add-on therapy in patients with severe asthma and/or bronchiectasis. Older age may predict good response in patients with severe asthma, whereas older age, male gender and a higher HRCT score for bronchiectasis may predict therapeutic response in patients with bronchiectasis only. Prospective controlled trials of neomacrolides in patients with severe asthma are needed to confirm these observations.

Keywords: neomacrolides, asthma, bronchiectasis

Introduction

Patients with severe asthma require high levels of medication to maintain good disease control or experience persisting symptoms despite multiple maintenance treatments [American Thoracic Society, 2000]. They account for only 5–10% of patients with asthma, but have a disproportionate impact on healthcare costs [Antonicelli *et al.*

2004; Godard *et al.* 2002]. Severe asthma is a heterogeneous disease and, based on the dominant cell type involved in the airway inflammation, the eosinophilic and noneosinophilic asthma (NEA) phenotypes have been described [Simpson *et al.* 2006, 2005; Wenzel, 2006; Miranda *et al.* 2004; Green *et al.* 2002]. Patients with NEA have increased sputum neutrophils and

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interleukin-8 (IL-8) levels and are less responsive to corticosteroid therapy than those with eosinophilic inflammation [Simpson *et al.* 2006, 2005]. Add-on therapies such as oral corticosteroids and anti-IgE monoclonal antibody therapy act specifically on eosinophilic inflammation and allergic IgE pathways and, consequently, offer less relief to patients with NEA [Berry *et al.* 2007]. Effective anti-inflammatory therapies for these patients are needed [Simpson *et al.* 2008].

Bronchiectasis is characterized by permanent dilatation of the bronchi that arises from chronic inflammation and bacterial colonization. Even though asthma and bronchiectasis are two different entities, their coexistence has been shown in many patients, especially in those with severe asthma [Oguzulgen *et al.* 2007]. As in patients with NEA, sputum analysis has shown raised concentrations of neutrophils and IL-8 in patients with non-cystic fibrosis (non-CF) bronchiectasis [Tsang *et al.* 2000; Richman et al. 1993]. Simpson and colleagues demonstrated that a persistent activation of the innate immune system may lead to this similar pattern of airway inflammation in both diseases [Simpson *et al.* 2007]. However, it remains uncertain whether bronchiectasis is a comorbidity in patients with asthma that makes the disease more difficult to control, or the result of increased levels of matrix metalloproteinases causing airway destruction and remodeling [Oguzulgen *et al.* 2007; Demedts *et al.* 2005; Takemura *et al.* 2004]. Non-CF bronchiectasis is being recognized with increasing frequency around the world and remains a major cause of excess respiratory morbidity [O'Donnell, 2008]. Since treatment is generally only partly successful in patients with bronchiectasis, improved anti-inflammatory medications are needed.

Beneficial effects of macrolides in asthma have been known for almost 50 years and in the past the reported therapeutic benefits were attributed to the inhibition of metabolism of exogenous steroids [Hrvacic *et al.* 2009; Fost *et al.* 1999]. Macrolide antibiotics possess antimicrobial activity against bacteria such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, which are associated with asthma exacerbations [Cosentini *et al.* 2008]. Currently, it is hypothesized that the efficacy of macrolides in patients with severe asthma results not only from their antimicrobial effects, but also from their immunomodulatory properties [Hrvacic *et al.* 2009]. Doses used in asthma

patients are lower than those for standard antibiotic therapy and studies showed an improvement in bronchial hyperresponsiveness independent of the action on exogenous steroid metabolism [Kostadima *et al.* 2004; Kamada *et al.* 1993; Ball *et al.* 1990].

Neomacrolides, such as clarithromycin and azithromycin, have been shown to have anti-inflammatory and/or immunomodulatory effects in addition to their antimicrobial properties [Giamarellos-Bourboulis, 2008; Lopez-Boado and Rubin, 2008; Shinkai *et al.* 2008; Culic *et al.* 2001]. Possible mechanisms of these anti-inflammatory effects include inhibition of inflammatory cytokine production, neutrophil migration and mucus hypersecretion [Crosbie and Woodhead, 2009; Lopez-Boado and Rubin, 2008; Tsai and Standiford, 2004]. Clinical improvement after treatment with macrolides in patients with diffuse panbronchiolitis and CF has been associated with these immunomodulatory effects [Kudoh *et al.* 1998; Koyama and Geddes, 1997; Sakito *et al.* 1996]. Reductions in IL-8 and neutrophil numbers in induced sputum after macrolide therapy have been demonstrated in several chronic airway diseases characterized by airway neutrophilia including diffuse panbronchiolitis, CF, bronchiolitis obliterans syndrome following lung transplantation and chronic obstructive pulmonary disease (COPD) [Vanaudenaerde *et al.* 2007; Verleden *et al.* 2006; Basyigit *et al.* 2004; Sakito *et al.* 1996; Oishi *et al.* 1994].

Since patients with NEA and/or bronchiectasis have increased neutrophils and IL-8 in their airways, the addition of macrolides to the treatment could be effective in patients with severe asthma and/or bronchiectasis. In a small monocentric randomized placebo-controlled trial, Simpson and colleagues showed a significant reduction in IL-8 and neutrophils in induced sputum of patients with severe asthma after treatment with clarithromycin for 8 weeks [Simpson *et al.* 2008]. Although the total asthma quality of life score improved with clarithromycin treatment, no significant changes in symptom scores or lung function were reported.

We therefore performed a retrospective observational cohort study and evaluated the safety and efficacy of add-on therapy with neomacrolides on pulmonary function tests and symptom scores in patients with severe asthma and/or bronchiectasis.

Methods

Design

This was a retrospective, single-center, observational cohort study, conducted at the Ghent University Hospital in Ghent, Belgium. A cohort of patients with severe asthma and/or bronchiectasis, receiving low-dose neomacrolides (clarithromycin or azithromycin) as add-on treatment for 3–8 weeks, was established. The ethics committee of Ghent University Hospital approved the study (IRB 2007/206). Patients were treated with clarithromycin ($n=97$) 500 or 250 mg once daily or with azithromycin ($n=11$) 500 or 250 mg three times a week. After 3–8 weeks of add-on treatment with low-dose macrolides, pulmonary function tests (in patients with asthma) and symptom scores (in both patient groups) were evaluated.

Patients

Male and female non-CF, adult patients with severe asthma and/or bronchiectasis, treated with neomacrolides as add-on treatment between June 2004 and September 2008, were selected. All patients were followed by a respiratory physician at the polyclinic for respiratory medicine at Ghent University Hospital. They were included in the care path for patients with severe asthma and/or bronchiectasis and were unresponsive to current maximal maintenance therapy. Therefore, a trial with low-dose neomacrolides was started as add-on therapy in this subgroup of patients, selected based upon persistent respiratory symptoms and/or frequent exacerbations. Immunocompromised patients and patients diagnosed with allergic bronchopulmonary aspergillosis were excluded. Diagnosis of asthma was made according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria [Bateman *et al.* 2008; Global Initiative for Asthma, 2006; Laszlo, 2006]. Based on clinical manifestations, pulmonary function tests, smoking history and high-resolution CT (HRCT) scan, patients were diagnosed with severe asthma (with or without bronchiectasis) or with bronchiectasis without asthma. After 3–8 weeks of treatment, patients were divided into responders and nonresponders based on the median improvement in forced expiratory volume in one second predicted (FEV₁; %) in asthma patients and symptom score in patients with bronchiectasis.

Assessments

Personal history, physical examination, pulmonary function tests, allergy skin prick tests, measurement of the fraction of nitric oxide in exhaled breath (FeNO), blood laboratory evaluations such as blood eosinophilia and total IgE, and high-resolution CT scan of the thorax were performed prior to the add-on treatment with macrolides in the same standardized way. Remodeling of proximal airways in severe asthma has been shown to be associated with impaired lung function and neutrophilic airway inflammation [Gupta *et al.* 2010]. We evaluated proximal airway remodeling by assessing the thickening of the right upper lobe apical segmental bronchus (RB1) on HRCT, which has been shown to be a good proxy for overall airway remodeling [Aysola *et al.* 2008]. After identifying RB1 on the HRCT images, the lumen area of RB1 (LA) and wall area (WA) were measured. Both measurements (LA and WA) were corrected for body surface area (BSA). The percentage wall area was calculated as follows: % WA = WA/TA $\times$ 100. In patients with bronchiectasis only, HRCT-scans were scored using an adaptive scoring system as described previously by Helbich and colleagues and Balla and colleagues [Helbich *et al.*; Balla *et al.*].

Spirometry was performed using a Viasys Sensormedics VMAX Spectra 22 according to the ATS/ERS task force guidelines for lung function testing [Laszlo, 2006]. Prior to therapy and after 3–8 weeks of treatment, four respiratory symptoms (including dyspnea, cough, nocturnal cough and sputum purulence/volume) were scored with a semiquantitative symptom score ranging from 0 to 2 and combined with a total symptom score ranging from 0 to 8. After 3–8 weeks, pulmonary function tests were performed only in the patients diagnosed with severe asthma. Severe exacerbations of asthma or bronchiectasis were defined as episodes needing use of systemic corticosteroids, disease-related emergency room visits or hospitalizations [Reddel *et al.* 2009].

Statistical methods

Results for continuous variables were expressed as mean $\pm$ standard deviation (SD), categorical variables were expressed as a proportion. Descriptive analyses evaluated sociodemographic and clinical variables of patients with asthma and patients with bronchiectasis only. A paired-sample Wilcoxon signed rank test was used to

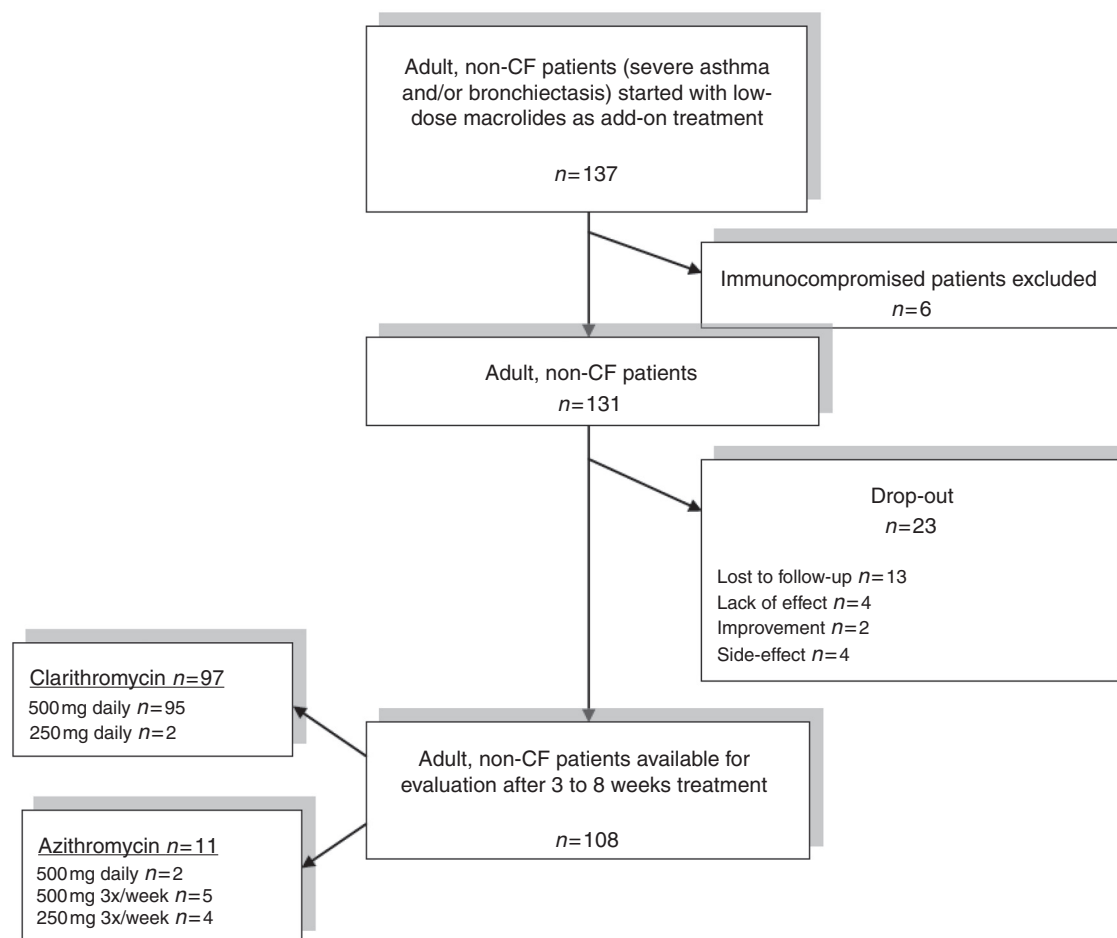


Figure 1. Flowchart of the patient population. CF, cystic fibrosis.

compare pulmonary function and symptom score between baseline and after 3–8 weeks of therapy. The Mann–Whitney *U*-test and chi-square test were used to compare continuous and categorical variables between asthma patients and patients with bronchiectasis and between responders and nonresponders. Multivariate logistic regression analysis was used to identify possible predictors for therapeutic response. All statistical analyses were performed using IBM SPSS Statistics, version 18 (SPSS Inc., Chicago, IL). A *p*-value of less than 0.05 was considered significant.

Results

Patients

A total of 137 adult, non-CF patients with severe asthma and/or bronchiectasis were treated with low-dose neomacrolides as add-on treatment. Four patients stopped macrolide treatment due to side effects, including rash (*n* = 1), diarrhea (*n* = 2) and dysgeusia (*n* = 1). After 3–8 weeks

of treatment, 108 patients were available for evaluation (Figure 1): clarithromycin was used by 97 patients and azithromycin by 11 patients. The clinical characteristics and medication use of the patients with asthma and patients with bronchiectasis are shown in Table 1. Patients with asthma were younger, had a lower FEV₁ (%) and FEV₁/forced vital capacity (FVC) ratio, and were more frequently allergic compared with patients with bronchiectasis only. In both groups there was a female predominance. Forty percent of the patients with asthma had a severe asthma exacerbation in the last 12 months and 62% of the patients with bronchiectasis had at least one lower respiratory tract infection (LRTI) in this period.

Lung function and symptom score in patients with severe asthma

Nearly all patients with asthma (45 of 47; 96%) were treated with (high-dose) inhaled corticosteroids and long-acting β_2 -agonists. In all 47 asthma patients, symptom scores were available

Table 1. Patient characteristics.

	Per protocol population		Asthma		Bronchiectasis		<i>p</i> -value
	<i>n</i>		<i>n</i>		<i>n</i>		Asthma vs bronchiectasis
Age (yr), mean (SD)	108	54.5(14.8)	47	50.5(14.3)	61	56.9(13.7)	0.031
Sex (% female)	108	57.3	47	57.4	61	59.0	0.870
(Ex) smoker (%)	108	26.7	47	25.5	61	26.2	0.935
Duration disease (yr), mean (SD)	55	17.3(17.0)	25	18.7(18.1)	30	20.3(17.3)	0.554
BMI (kg/m ²), mean (SD)	107	25.1(4.8)	47	215.0(5.2)	60	24.6(4.3)	0.148
Symptom score, mean (SD)	108	4.6(1.6)	47	5.0(1.7)	61	4.6(1.3)	0.098
FEV ₁ (L), mean (SD)	105	24(0.9)	47	2.2(0.8)	58	2.5(1.0)	0.225
FEV ₁ (%), mean (SD)	105	81.5(24.7)	47	75.0(21.0)	58	85.7(26.1)	0.014
FEV ₁ /FVC ratio, mean (SD)	105	64.3(15.0)	47	62.0(14.7)	58	66.6(15.1)	0.043
FeNO (ppb), mean (SD)	55	22.4(2.5)	30	24.6(2.8)	25	17.4(2.7)	0.327
Allergy	84	554	41	68.3	43	37.2	0.004
Blood eosinophilia (/μl), mean (SD)	81	264.5(408.5)	40	404.5(559.5)	41	185.5(128.3)	0.147
LRTI (%)	108	56.5	47	44.7	61	62.3	0.068
Exacerbations (%)	108	28.2	47	40.4	61	19.7	0.018
Medication Use:							
ICS (%)	108	13.0	47	14.9	61	11.5	0.600
LABA (%)	108	3.1	47	6.4	61	1.6	0.196
ICS/LABA(%)	108	71.0	47	89.4	61	62.3	0.001
AC (%)	108	23.7	47	25.5	61	18.0	0.345
Theophylline (%)	108	15.3	47	27.7	61	8.2	0.007
LTRA (%)	108	13.0	47	23.4	61	6.6	0.012
Daily use SABA (%)	103	23.0	42	35.7	61	18.0	0.042
OCS (%)	108	14.5	47	19.1	61	9.8	0.165

Symptom score: dyspnoea [0-2] + cough [0-2] + nocturnal cough [0-2] + sputum purulence/volume [0-2].

FeNO: measurement of the fraction of nitric oxide in exhaled breath.

Allergy: positive skin prick test or RAST-test for one or more allergens.

LRTI: lower respiratory tract infection, pneumonia or more than one antibiotic course for respiratory infection during the past 12 months.

Exacerbation: episodes needing use of systemic corticosteroids (tablets or injection) or an increase from a stable maintenance dose for at least 3 days, airway-related emergency room visits or hospitalizations.

ICS: Inhaled corticosteroids **LABA:** long acting β_2 agonists **AC:** anticholinergics **LTRA:** leukotriene receptor antagonists **SABA:** short acting β_2 agonists **OCS:** oral corticosteroids.

after 3–8 weeks. Total symptom score decreased significantly ($p < 0.001$) with a mean procentual improvement of 58.0%. In 37 of the 47 patients with severe asthma, pulmonary function tests were available after 3–8 weeks of add-on treatment. The mean prebronchodilatation FEV₁ (%) raised significantly ($p = 0.001$) from 72.5% to 82.2%. The median difference in FEV₁ (%) was 7.0%. Responders were defined as patients having more than 7.0% improvement in FEV₁ (%).

Symptom score in patients with bronchiectasis only

Symptom scores for dyspnea, cough, nocturnal cough and sputum purulence and volume all decreased significantly and as a result the mean total symptom score decreased significantly from 4.61 to 1.93 ($p < 0.001$). The median procentual improvement in total symptom score was 60%.

Responders were defined as patients having more than 60% improvement in total symptom score after 3–8 weeks of therapy.

Predictors of therapeutic response

In the subpopulation of patients with severe asthma, responders were older (55.0 *vs.* 47.0 years, $p = 0.042$) and tended to have a longer duration of disease (29.0 *vs.* 9.0 years, $p = 0.052$) compared with nonresponders. Although not statistically significant, responders had a higher BMI, lower FEV₁ and less allergy. There was no significant difference in percentage wall area between responders and nonresponders in patients with severe asthma. Clinical characteristics of responders and nonresponders in the asthma population are compared in Table 2.

In the patients with bronchiectasis only, responders were older (61.0 *vs.* 53.0 years, $p = 0.004$),

Table 2. Characteristics of responders and non-responders in patients with severe asthma.

Patients with asthma	Responder		Non-responder		<i>p</i> -value
	<i>n</i>		<i>n</i>		
Age (yr), mean (SD)	19	55.3(16.4)	18	46.5(13.1)	0.042
Sex (% female)	19	58.0	18	50.0	0.630
Duration of disease (yr), mean (SD)	7	29.1(23.0)	14	8.9(8.8)	0.052
(Ex)smoker (%)	19	31.6	18	27.8	0.800
BMI (kg/m ²), mean (SD)	19	27.0(6.0)	18	24.9(4.9)	0.202
Symptom score, mean (SD)	19	5.1(1.6)	18	5.1(1.2)	0.686
FEV1(L), mean (SD)	19	2.0(0.7)	18	2.4(0.8)	0.136
FEV1(%), mean (SD)	19	70.6(20.4)	18	74.4(23.7)	0.533
FEV1Z1/FEVC(ratio), mean (SD)	19	59.4(13.1)	18	61.9(18.3)	0.681
FeNO(ppb), mean (SD)	13	31.6(2.6)	10	20.4(2.5)	0.264
Wall area percentage (%), mean (SD)	16	67.19(7.6)	13	70.16(9.8)	0.335
Allergy (%)	17	58.8	16	81.2	0.161
Blood eosinophilia(/ <i>κ</i> l), mean (SD)	16	518.8(7f25865.6(43.6(16)-4865.626947.9f25865.6(43.6620.630)]T/131Tf822.067-			

Table 3. Characteristics of responders and non-responders in patients with bronchiectasis only.

Patients with bronchiectasis only	Responder		Non-responder		<i>p</i> -value
	<i>n</i>		<i>n</i>		
Age (yr), mean (SD)	34	60.6(15.3)	26	52.8(9.8)	0.004
Sex (% female)	34	47.1	26	73.1	0.043
Duration of disease (yr), mean (SD)	18	19.7(15.2)	11	22.7(21.0)	1.000
(Ex)smoker (%)	34	26.5	26	26.9	0.969
BMI (kg/m ²), mean (SD)	34	24.2(3.5)	26	25.2(5.1)	0.932
Symptom score, mean (SD)	33	4.6(1.5)	26	4.8(1.6)	0.652
FEV1(L), mean (SD)	32	2.5(0.9)	25	2.3(1.1)	0.285
FEV1(%), mean (SD)	32	87.1(23.0)	25	83.5(30.5)	0.748
FEV1/FVC (ratio), mean (SD)	32	66.3(15.8)	25	66.6(14.5)	0.910
FeNO (ppb), mean (SD)	13	19.1(3.5)	12	15.1(1.8)	0.327
HRC-T score, mean (SD)	23	6.4(4.1)	24	4.6(4.3)	0.053
Allergy (%)	23	39.1	20	35.0	0.780
Blood eosinophilia(/ <i>κ</i> l), mean (SD)	29	195.1(168.3)	11	167.3(198.8)	0.879
Resp. infections as a child (%)	23	43.5	17	58.8	0.337
ENT complaints (%)	34	47.1	26	38.5	0.505

Symptom score: dyspnoea (0-2) + cough (0-2) + nocturnal cough (0-2) + sputum purulence/volume (0-2).
Allergy: positive skin prick test or RAST-test for one or more allergens.
FeNO: measurement of the fraction of nitric oxide in exhaled breath.
ENT: Ear, nose, and throat.

but there was no difference in duration of disease. Responders were more frequently male (53 *vs.* 27%, *p* = 0.043). There was a nonsignificant trend towards higher HRCT score for bronchiectasis in responders (6.4 *vs.* 4.6; *p* = 0.053). Characteristics of responders and nonresponders in patients with bronchiectasis are compared in Table 3. The multivariate logistic regression analysis showed that age and male sex were

independent predictors for treatment response in patients with bronchiectasis. The odds ratio (OR) for age was 1.06 with 95% confidence interval (CI) 1.01–1.12; OR for male sex was 4.47 with 95% CI 1.14–17.51.

Discussion

In this retrospective observational study, we report a significant improvement in pulmonary

function and symptom score in patients with severe asthma after 3–8 weeks of add-on treatment with clarithromycin or azithromycin. Previous studies on the use of macrolides in patients with asthma have shown conflicting results, probably in part due to the heterogeneity of the study populations [Richeldi *et al.* 2005]. In a study of 55 patients with chronic stable asthma, Kraft and colleagues found improvement in FEV₁ only in patients who were PCR+ for *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* [Kraft *et al.* 2002]. Two studies have shown significant reductions in bronchial hyperresponsiveness in patients with asthma after 8 weeks of treatment with clarithromycin, but neither showed any significant change in FEV₁ [Kostadima *et al.* 2004; Amayasu *et al.* 2000]. In a more recent study, Simpson and colleagues showed improvement in quality of life in patients with severe refractory asthma, but no improvement in bronchial hyperresponsiveness or FEV₁ was observed [Simpson *et al.* 2008].

Simpson and colleagues have demonstrated that neutrophilic airway inflammation is associated with a good response to clarithromycin [Simpson *et al.* 2008]. Recently, using cluster analysis in the Severe Asthma Research Program (SARP), five distinct clinical phenotypes of severe asthma have been identified [Moore *et al.* 2010]. Interestingly, cluster 3, a unique group of mostly older obese women with late-onset nonatopic asthma, and cluster 5, a group with severe airflow obstruction and late-onset nonatopic asthma, have the highest percentages of neutrophils in induced sputum [Moore *et al.* 2010]. Older age, female predominance, overweight and the relatively low prevalence of allergy, as observed in our patients with severe asthma, are in line with the clinical characteristics of clusters 3 and 5. These clinical characteristics (older age and less allergy) are even more pronounced in the responders, suggesting that neutrophilic airway inflammation might predominate in these patients with severe asthma and explain the therapeutic benefit of macrolides. However, in our study, no examination of airway inflammation as a response determinant or outcome measure has been made.

In patients with bronchiectasis only, we observed a significant improvement of dyspnea, cough, nocturnal cough, sputum purulence/volume and total symptom score. Despite the fact that trials of macrolide treatment in non-CF bronchiectasis

are limited, there is some consistent evidence of a decrease in exacerbation frequency and sputum volume [Crosbie and Woodhead, 2009; Cymbala *et al.* 2005]. In a prospective open-label study on 39 adult patients, Davies and Wilson reported a decrease in exacerbation frequency, in the need for i.v. antibiotics and in symptoms after treatment with low-dose azithromycin [Davies and Wilson, 2004]. Other studies have been conducted in children or with macrolides other than azithromycin and clarithromycin [Yalcin *et al.* 2006; Tsang *et al.* 1999; Koh *et al.* 1997]. These studies correspond with our findings that sputum volume or purulence was decreased after neomacrolide therapy.

In patients with bronchiectasis, we found that responders were older, more frequently male and had a higher HRCT score for bronchiectasis compared with nonresponders. After correcting for covariates using multivariate logistic regression analysis, age (OR age 1.06, 95% CI 1.01–1.12) and male sex (OR male sex 4.47, 95% CI 1.14–17.51) appeared to be independent predictors for good response on neomacrolide therapy. We put forward the hypothesis that a male predominance in responders might explain the connection between non-CF bronchiectasis and diffuse panbronchiolitis (DPB), which is an idiopathic inflammatory airway disease, most common in eastern countries, that evolves to bronchiectasis, respiratory failure and death when untreated [Poletti *et al.* 2006]. As in patients with bronchiectasis, the airways in patients with DPB are frequently colonized by *Pseudomonas aeruginosa* and have increased numbers of neutrophils and cytokines as IL-8 [Poletti *et al.* 2006; Koyama and Geddes, 1997; Sakito *et al.* 1996]. Thus, DPB is linked to bronchiectasis in its pathophysiology and in its evolution. Since DPB is slightly more frequent in males [Poletti *et al.* 2006] and since macrolides are very effective in the treatment of DPB [Kadota *et al.* 2003; Koyama and Geddes, 1997], the link between bronchiectasis and DPB could well explain the male predominance for therapeutic response observed in our study.

As in all observational studies, our study has several limitations. First, the retrospective nature of our study could be associated with poorer data quality (e.g. missing data) in comparison with prospective studies. Since biological parameters as FeNO and blood eosinophilia were not

determined repeatedly in this study, we focused on clinically relevant outcomes, i.e. pulmonary function and symptom scores. Second, the statistical analyses are based on the per protocol population, implicating that results are only available from those patients who had a re-evaluation after 3–8 weeks. Third, the uncontrolled design of the study likely overestimates the treatment effects. Finally, this study was conducted in a single center and therefore these findings should be replicated in larger multicenter controlled studies in patients with severe asthma. Despite these limitations, observational studies provide useful and important information about treatment effects in a ‘real-world’ setting in addition to randomized controlled trials.

In summary, we conclude that neomacrolides may be useful as add-on therapy in patients with severe asthma and/or bronchiectasis. Older age in patients with severe asthma and older age, male gender and a higher HRCT score for bronchiectasis in patients with bronchiectasis only may predict therapeutic response. Future large, randomized controlled studies are required to gather more evidence for the implementation of macrolides in these patients. We therefore refer to the ongoing multicenter double-blind placebo-controlled randomized AZithromycine in Severe ASThma study (AZISAST) (see www.clinicaltrials.gov).

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Conflict of interest statement

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