Macrolide maintenance treatment for bronchiectasis
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CHAPTER 5
Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial.

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Abstract

- Context: Macrolide antibiotics have been shown to be beneficial in cystic fibrosis (CF) and diffuse panbronchiolitis (DPB), and earlier findings also suggest a benefit in non-CF bronchiectasis.

- Objective: To determine the efficacy of macrolide maintenance treatment for adults with non-CF bronchiectasis.

- Design, Setting and Participants: A randomized double-blind, placebo-controlled multicenter trial between April 2008 and September 2010 in 89 out-patients in 14 hospitals in the Netherlands with ≥ 3 lower respiratory tract infections in the preceding year (ClinicalTrials.gov Identifier: NCT00415350).

- Intervention: Azithromycin (250 mg daily) or placebo for 12 months.

- Main Outcome Measures: The number of infectious exacerbations during 12 months of treatment. Secondary endpoints included lung function, sputum bacteriology, inflammatory markers, adverse effects, symptom scores and quality of life (QoL).

- Results: 43(52%) participants received azithromycin and 40(48%) placebo and were included in the modified intention to treat analysis. At end of study, the median number of exacerbations in the placebo group was 2(IQR 1-3), compared to 0(IQR 0-1) in the azithromycin group (p< 0.0001). 32 (80%) of the placebo- versus 20 (46%) of azithromycin-treated individuals had at least one exacerbation (HR = 0.29 (95%CI: 0.16-0.51). In a mixed model analysis, change in FEV$_1$(% predicted) over time differed between groups (F (1,78.8)=4.085, p=0.047), showing an increase of 1.03% per three months in the azithromycin group, while decreasing with 0.10% per three months  in the placebo group. Gastrointestinal adverse effects occurred in 40% of patients in the azithromycin group, and 5% in the placebo group; RR: 7.44 (CI: 0.97-56.88), for abdominal pain; and RR 8.36 (CI: 1.10-63.15) for diarrhea, but without need for discontinuation of study treatment. A macrolide resistance rate of 88% was noted in azithromycin-treated individuals, as compared to 26% in the placebo group.

- Conclusions: Among adults with non-CF bronchiectasis, the daily use of azithromycin for 12 months compared with placebo resulted in a lower rate of infectious exacerbations.

Introduction

Bronchiectasis is radiographically characterized by pathologic dilatation and mucosal thickening of the small and medium-sized bronchi. Structural abnormality of the bronchial wall causes impaired clearance of the lower airways leading to chronic bacterial infection and inflammation, a process that has been referred to as a ‘vicious circle’. If progressive, this may lead to respiratory failure and the need for lung transplant or death. The course of the disease is highly variable. Nearly symptom free periods intersperse with infectious exacerbations, characterized by worsening of symptoms of productive cough, hemoptysis and dyspnea. Frequent exacerbations have a major impact on quality of life. Macrolide antibiotics have anti-bacterial and anti-inflammatory properties which conceivably would provide effective treatment of bronchiectasis. The effectiveness of macrolide maintenance therapy in reducing disease activity, exacerbations and decline in lung function has been demonstrated in cystic fibrosis (CF).

Efficacy of long-term low-dose macrolide treatment in non-CF bronchiectasis had first been studied in small, mostly non-randomized studies, showing a positive effect on exacerbation frequency, sputum volume and inflammatory markers. Recently, Wong et al reported an important reduction of infectious exacerbations with azithromycin in non-CF bronchiectasis. Their ‘EMBRACE’ trial included 141 patients with non-CF bronchiectasis who received six months of either azithromycin (500 mg 3x/ wk) or placebo.

We initiated a multicenter trial to investigate whether one year of long term low dose macrolide treatment added to standard therapy is effective in reducing exacerbation frequency in non-CF bronchiectasis.

Methods:

Study design: The Bronchiectasis and long term Azithromycin Treatment (BAT)-trial was a multicenter, double-blind, placebo-controlled, parallel-group study with equal randomization [1:1], conducted in the Netherlands (14 sites) between April 2008 and September 2010. The study protocol was reviewed and approved by the ethical review committees of all study sites and the study was performed in accordance with the Good Clinical Practice (GCP) Guidelines, the International Conference on Harmonization (ICH) Guidelines, and the most recent version of the Declaration of Helsinki. This study adhered to the consolidated standards for the reporting of randomised controlled trials (CONSORT).

The BAT trial was registered at Clinicaltrials.gov, registration no: NCT00415350.

Participants: Patients who met the inclusion criteria were ≥18 years of age and had non-CF
bronchiectasis diagnosed by plain bronchography or high resolution computed tomography (HRCT). All patients had had a minimum of three lower respiratory tract infections (LRTI) treated with oral/IV antibiotics in the preceding year and had at least one sputum culture yielding one or more bacterial respiratory pathogens in the year prior to study entry. Patients were excluded if they received prolonged macrolide therapy (> 4 weeks) during the previous three months, oral/IV courses of corticosteroids within 30 days of screening or any antimicrobial treatment for a LRTI in the last two weeks. The use of long-term maintenance antibiotics or low-dose steroids was permitted during the study. Patients with a known allergy or intolerance to macrolides; women with child-bearing potential avoiding contraceptives, as well as lactating women; and patients with liver disease or with elevated transaminases: aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) ≥ the upper limit of normal were also excluded from the study.

Setting: Patients were recruited from out-patient clinics at each of the 14 study sites by their pulmonary physician or the investigator. After patients had given written informed consent, their medical history was reviewed and if eligible, were randomized.

Interventions: Following randomisation, patients were observed for clinical stability for two weeks, after which they received either oral azithromycin 250 mg once a day or placebo for the subsequent 52 weeks. Due to lack of a standard treatment regimen, the 250 mg regimen was chosen in order to increase patient compliance by daily administration and to minimize side effects by choosing a low daily dosage. Compliance was monitored by counting empty blisters of study medication at each study visit by the investigator.

Procedures and outcomes: The primary outcome was the number of infectious exacerbations during the 52-week treatment period. An infectious exacerbation was defined as an increase in respiratory symptoms, requiring antibiotic treatment. Although the original protocol required the inclusion of antibiotic and steroid treated events, we decided to omit the small number of events not treated with antibiotics in the analysis of our primary endpoint. Two types of exacerbations were included in the primary endpoint: a protocol defined exacerbation (PDE) and a non-PDE (NPDE). An exacerbation was considered a PDE when at least four of the following nine symptoms, signs or findings were present: (1) change in sputum production (consistency, colour, volume, or hemoptysis); (2) increased dyspnoea (chest congestion or shortness of breath); (3) increased cough; (4) fever (>38°C); (5) increased wheezing; (6) decreased exercise tolerance, malaise, fatigue, or lethargy; (7) FEV1 or FVC decreased by at least 10% from a previously recorded value; (8) radiographic changes indicative of a new pulmonary infectious process; or (9) changes in chest sounds. A NPDE was noted when a patient had less than four of the above abnormalities.

On weekly diary cards, patients were asked to report whether they received antibiotics for an exacerbation in the preceding week and if so, which of the above mentioned findings 1 – 6 applied to that particular exacerbation. Findings 7-9 were evaluated by the treating physicians.

All treating physicians (general practitioners and pulmonary physicians) were instructed to report every exacerbation to the researchers by phone or fax. On every follow-up visit, patients were specifically asked about exacerbations in the past three months. At end of study, a member of the research team visited each participant in the respective hospitals. On these visits, the researcher had full insight in the patient’s medical files and double-checked these for reports of infectious exacerbations and/or courses of antibiotics.

In case of an infectious exacerbation, the choice of the antibiotic regimen was left to the discretion of the attending physician who was generally not a member of the trial team and always blinded to the patient’s treatment allocation. Treatment was started based on the patient’s symptoms and guided by in vitro susceptibility data. Study medication was continued during an exacerbation if possible.

Secondary endpoints included lung function, serum C-reactive protein (CRP), white blood cell count (WBC), microbiological evaluation, symptoms measured by a LRTI--Visual Analogue Scale (VAS) (eFigure 2), health-related quality of life (QoL) as measured by St. George’s Respiratory Questionnaire (SGRQ) and adverse events (eFigure 3).

After randomisation and a two week run in period, patients were followed every three months during the 52-week treatment period for blood sampling, lung function tests, questionnaires, sputum cultures and safety checks and once at the end of the run-out period (eFigure 1). Laboratory tests included measurement of serum CRP, WBC and measurement of ASAT and ALAT. Lung function measurements were performed according to European Respiratory Society standard criteria. Sputum samples were collected at each visit and submitted for culture and susceptibility testing at the Medical Centre Alkmaar (see: eMethods).

Symptoms were measured using the LRTI-VAS (Lower Respiratory Tract Infections -Visual Analogue Scale), a symptom score, specifically designed to investigate common symptoms in patients with bronchiectasis. (eMethods; eFigure 2). This scale consists of a set of horizontal lines with two anchor points, one at each extreme, each line representing a different symptom. Each symptom is scored from 1 to 10, the subjects being unaware of the numbers. Higher scores indicate more severe symptoms. Five symptom domains were scored: dyspnoea, fatigue, cough, chest pain and sputum colour. Separate scores were calculated for each symptom with a total score consisting of all symptom scores added.
The SGRQ - a condition-specific questionnaire - was used to measure health related QoL (HRQoL) (eFigure 3). Its 76 items are partitioned into three sections (Symptoms, Activity, Impact), which are scored separately and can be added up to provide a total score, ranging from 0 to 100%, zero indicating no impairment of quality of life. A difference of 4 points or more is considered clinically significant. The SGRQ requires about 10 minutes to complete; it has been validated for use in bronchiectasis patients.

Diary cards, with weekly reports of symptoms, courses of antibiotics and adverse effects (specifically addressing gastro-intestinal, skin and ‘other’ adverse effects), were completed by all participants during the entire study period. An additional questionnaire evaluating hearing complaints was sent to all participants at end of study.

After one year of treatment with placebo or azithromycin, patients had variable run-out period of at least 90 days. When establishing the between-group differences for exacerbation frequency in the run-out phase, only data collected within 90 days after discontinuing study treatment was used.

Randomisation and masking: On the first study visit, all patients were seen by the investigator and sequentially assigned a subject identification code with double blinded allocation to either azithromycin or placebo treatment. Placebo tablets were manufactured by a licensed trial pharmacy and were indistinguishable from azithromycin with respect to appearance, feeling and taste.

Placebo and azithromycin tablets were provided in identical, individually numbered boxes, each box containing a year’s supply of study medication for one participant. Numbers on the boxes matched a treatment allocation, in accordance with a computer-generated allocation sequence which was kept in a safe place in the pharmacy providing the study medication. We used permuted block randomization, with equally sized blocks of 10. Randomization was performed centrally, no stratification for factors such as exacerbation frequency or study center was applied.

Sample size calculation: The primary hypothesis was that prolonged treatment with azithromycin would cause ≥33% (SD1.5) reduction of the number of exacerbations per patient, decreasing the yearly number of exacerbations per patient from 3 to 2. In three small trials, exacerbations were reduced from 3-10 / year to 1-5 during azithromycin therapy. In a study with 24 adult non-CF bronchiectasis patients, erythromycin reduced exacerbations from 4 (2-11) to 2 (0-8) year. Azithromycin in CF reduced exacerbations from 3-4 to 1.5- 1.6 / year. These limited data available combined with our clinical experience in these patients made us assume that azithromycin would at least reduce the number of exacerbations by one third.

We calculated that a sample size of 36 participants in each group was required to detect this reduction with a one-sided significance level of 0.05 and a power of 80%, and planned to include 90 patients, assuming 20% dropout. One-sided testing was considered appropriate in view of the favourable results of this treatment modality in previous, smaller trials.

Statistical methods

Statistical analysis was performed on the modified intent-to-treat population, defined as all randomized participants who received at least 1 dose of study drug. Patients that were randomized but afterwards appeared not to fulfil in- and exclusion criteria were not started on study medication and were excluded from analysis. Comparisons of parameters between treatment groups were calculated with a t-test if distributed normally, otherwise with a Mann-Whitney U test. There were no patients with missing information on exacerbations during intervention.

Statistical significance in change of FEV₁ % predicted and FVC % predicted due to treatment was calculated with a linear mixed-model analysis. The effect of time on outcome variables was checked for linearity by means of plots and model fits with quadratic and cubic functions of time. Change in quality of life was analysed using linear mixed-model analysis as well.

Time was entered as an interval variable. Therapy and sex were entered stepwise as fixed effects. Predictors remained in the regression equation if the model fit increased significantly. Thereafter, random effects were explored for intercept (patients) and slope (time and patients). If random effects did not change the model fit significantly, a fixed effect was assumed. Residuals followed a normal distribution. Sex and age were considered as confounder or effect modifier and reported in the results if significant. The same method was used for the evaluation of the CRP, the SGRQ and the VAS-score. p < 0.05 was considered statistically significant (one-sided). The software package SPSS 18 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

One planned safety analysis, that was performed by an independent statistician after enrolment of 45 patients, showed no significant differences with regard to adverse effects and therefore the study was continued as planned. Between-group comparisons for adverse events were performed, but this study was not powered for safety analysis.
Results

A total of 83 patients were randomly assigned to azithromycin or placebo treatment and included in the modified intention to treat population (figure 1). Participation rate among eligible patients was 62%, reasons for exclusion are presented in figure 1. From empty blister counts we estimated that patients adhered 96.5% of the time in the azithromycin group and 98.0% of the time in the placebo group. One patient in each group discontinued intervention because of adverse effects (figure 1).

Figure 1. Patient flow chart

Primary endpoint

A total of 117 exacerbations (100 of which PDE, 17 non-PDE) treated with antibiotics were reported during one year of treatment, 78 of which occurred in the placebo group. The median number of exacerbations during the treatment period in the placebo group was 2 (IQR 1-3), compared to a median number of exacerbations in the azithromycin group of 0 (IQR 0-1), p< 0.0001 (MWU) (table 2). Of the 40 participants on placebo, 32 (80%) had at least one exacerbation during the study period. In the 43 participants on azithromycin, 20 (46.5%) had had at least one exacerbation in the same period, yielding an absolute risk reduction of 33.5% (95% CI 14.1 - 52.9). The number of patients needed to treat with azithromycin to maintain clinical stability is 3.0. Time to first exacerbation in a post-hoc analysis differed, with a hazard ratio of 0.29 (95%CI:0.16-0.51) for participants on azithromycin compared to placebo (figure 2A). Time until the first exacerbation did not differ in the run-out period (HR 0.56 (95% CI; 0.26-1.19) (figure 2B).
Lung function:

Change in FEV1% predicted over time was different for patients on placebo compared to azithromycin, F (1,78.8)=4.085, p=0.047. In patients on azithromycin, FEV1% predicted increased 1.03 per 3 months (intervals of visits). In patients on placebo FEV1% predicted decreased 0.10 per 3 months.

Change in FVC% predicted over time was different for patients on placebo compared to azithromycin, F (1,78.6)=5.9, p=0.018. In patients on azithromycin, FVC % predicted increased 1.33 per 3 months (intervals of visits). In patients on placebo FVC% predicted decreased 0.30 per 3 months.

(details of the mixed model analysis are provided in eResults).

Inflammatory markers:

Change in serum CRP levels and white blood cell count during the study period was not significantly different between both treatment groups.

Microbiology

A total of 437 sputum samples were cultured for microbiology, which yielded one or more pathogens on 339 occasions. The microbiological profile did not differ significantly between azithromycin-treated and placebo-treated patients at baseline and after 1 year of treatment. Numbers of cultures positive for *P. aeruginosa* did not differ between treatment groups or between start and end of study (table 2).

*H. influenzae*, *S. pneumoniae*, *S. aureus*, *M. catarrhalis*, *H. parainfluenzae* were most frequently encountered, together comprising 87% of the total number of pathogens. 75% of these pathogens were tested for macrolide resistance.

At baseline, resistance patterns were comparable between both groups (35% macrolide resistance in 8 patients in the azithromycin group against 27.5% in 9 patients in the placebo group; p = 0.75). During treatment, 53 out of 60 (88%) pathogens tested for sensitivity in 20 patients in the azithromycin group became macrolide resistant against 29 out of 112 (26%) in 22 patients in the placebo group (p < 0.0001; Student’s T-test; eResults table 1).
Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin (n=43)</th>
<th>Placebo (n=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, SD)</td>
<td>59.9 (12.3)</td>
<td>64.6 (9.1)</td>
<td>0.051</td>
</tr>
<tr>
<td>Female sex (No,% )</td>
<td>25 (63)</td>
<td>28 (65)</td>
<td></td>
</tr>
<tr>
<td>Nr of exacerbations in year before study entry (median, IQR)</td>
<td>4.0 (3-9)</td>
<td>5.0 (3-12)</td>
<td>0.32</td>
</tr>
<tr>
<td>Aetiology of bronchiectasis:*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post infectious</td>
<td>15 (35)</td>
<td>13 (33)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>12 (28)</td>
<td>15 (38)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>7 (16)</td>
<td>7 (18)</td>
<td></td>
</tr>
<tr>
<td>Auto-immune disease</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Common variable immune disorder (CVID)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Primary ciliary dyskinesia (PCD)</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Yellow Nail Syndrome</td>
<td>0</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mechanical obstruction</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Alpha-1- antitrypsin deficiency</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Percent predicted FEV1</td>
<td>77.7 (24.4)</td>
<td>82.7 (27.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Percent predicted FVC</td>
<td>91.9 (24.4)</td>
<td>98.5 (23.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>CRP (mmol/l) (median, IQR)</td>
<td>5.0 (2-11.3)</td>
<td>4.5 (2-15.3)</td>
<td>0.43</td>
</tr>
<tr>
<td>WBC count</td>
<td>8.1 (2.7)</td>
<td>8.1 (3.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>SGRQ total score</td>
<td>40.6 (19.4)</td>
<td>40.2 (20.9)</td>
<td>0.94</td>
</tr>
<tr>
<td>LRTI-VAS total score</td>
<td>37.5 (10)</td>
<td>17.9 (8.0)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Baseline sputum microbiology:
- Haemophilus influenzae 13 (30) | 9 (23) 
- Staphylococcus aureus 4 (9) | 9 (23) 
- Pseudomonas aeruginosa 6 (14) | 6 (15) 
- Hearing impairment previous to study entry: † | 12 (28) | 11 (28) 
- Body mass index 23.0 (3.4) | 24.5 (4.0) | 0.068 |

Abnormalities on auscultation:
- Crackles 20 (47) | 11 (28) 
- Rhonchi 8 (19) | 10 (25) 
- Wheezing 7 (16) | 6 (15) 
- Dullness 0 | 1 (3) 

Smoker
- Current 1 (2) | 1 (3) 
- Former 19 (44) | 17 (43) 

Treatment previous to study entry (No,%):
- Inhaled corticosteroids‡ | 38 (88.4) | 32 (80) 
- Long-acting β-agonist‡ | 34 (79) | 30 (75) 

Data are n(%) or mean (SD) unless otherwise indicated. FEV1 = forced expiratory volume in 1 sec. FVC = forced vital capacity. SGRQ = St George’s respiratory questionnaire. LRTI-VAS= lower respiratory tract infection- visual analogue score.
* As described by the treating pulmonary physician
† patient reported hearing impairment
‡ Treatment started before study entry and continued during the study period
§ Any technique taught by a physiotherapist and performed by the patient in order to evacuate sputum
1. student’s T-test
2. Mann Whitney U test

Quality of life (QoL) and patient-reported symptoms

Quality of Life (QoL) as measured by SGRQ showed a larger decrease of the total score (indicating better QoL) in patients on azithromycin at the end of treatment as compared to patients on placebo (p=0.046). QoL by SGRQ was measured at the start of intervention and after 6 and 12 months. In patients on azithromycin, SGRQ total score decreased -6.09 per 6 months. This means that in the mixed model patients had average decrease in SGRQ score of 2 * -6.09 = 12.18 after one year of treatment. In patients on placebo, SGRQ total score decreased -2.06 per 6 months. In a post-hoc analysis, when comparing SGRQ total scores at start of treatment with total scores after one year, 28 (64%) patients in the azithromycin group had an improvement of 4 units, as compared to 18 (46%) in the placebo group.

Quality of life as measured by the LRTI-VAS score showed a larger decrease of the total score (indicating less symptoms) in patients on azithromycin at the end of treatment as compared to patients on placebo (p= 0.047). In patients on azithromycin, total VAS score decreased with 1.11 per 3 months. This means that in the mixed model patients had an mean decrease of total VAS score of 4 (follow-up visits until end of treatment) * 1.11 = 4.44 after one year of treatment. In patients on placebo VAS total score decreased with 0.056 per 3 months. (for more detailed results of the mixed model analysis , see eResults).
Safety

Among the adverse events reported, only abdominal pain and diarrhea showed an elevated relative risk (table 2). These complaints, mostly occurring in the first weeks of treatment and subsequently subsiding, were mild and did not result in discontinuation of treatment. One patient in each group discontinued intervention because of a suspected adverse effect (2.3% vs 2.5%); one patient in the placebo group (2.5%) developed a severe rash and was subsequently diagnosed with psoriasis, one patient in the azithromycin group (2.3%) complained about progressive fatigue, which did not resolve after discontinuation of treatment. There were no differences in ASAT or ALAT between study groups during treatment.

During treatment, 1 patient in the azithromycin group had an infectious exacerbation requiring admission, 2 patients had surgery (sinus surgery (FESS) and because of uterus prolapse), 1 was diagnosed with hyperthyroidism and 1 with insulin dependent diabetes mellitus. In the placebo group, 2 patients had an infectious exacerbation requiring admission, 3 had surgery (2 FESS and 1 cholecystectomy), 1 was diagnosed with lung carcinoma, 1 hospitalized for suspected malignancy and 1 received pharmacological treatment for depression.

Table 2. Exacerbation frequency and secondary outcomes after one year of study treatment by treatment group

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin (n=43)</th>
<th>Placebo (n=40)</th>
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<tbody>
<tr>
<td>No. of exacerbations</td>
<td>Total</td>
<td>36 (31)</td>
</tr>
<tr>
<td></td>
<td>of which PDE</td>
<td>31 (86)</td>
</tr>
<tr>
<td></td>
<td>of which non PDE</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0 (0-1)</td>
<td>2 (1-3)</td>
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<tr>
<td></td>
<td>Mean</td>
<td>0.84 (1.13)</td>
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<table>
<thead>
<tr>
<th>No. of exacerbations per patient</th>
<th>Azithromycin (n=43)</th>
<th>Placebo (n=40)</th>
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<tbody>
<tr>
<td>0</td>
<td>23 (54)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>1</td>
<td>10 (23)</td>
<td>8 (20)</td>
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<tr>
<td>2</td>
<td>6 (14)</td>
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<td>3</td>
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<tr>
<td>4</td>
<td>2 (5)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>1 (3)</td>
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<tr>
<td>CRP level (mg/L)</td>
<td>2.6 (1.5-7.0)</td>
<td>3.9 (2.0-6.15)</td>
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Table 2. Continued

<table>
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<tr>
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<th>Relative risk (95% CI)</th>
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<td>Adverse events</td>
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<tr>
<td>No adverse events</td>
<td>25 (58)</td>
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<tr>
<td>Nausea</td>
<td>6 (14)</td>
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<tr>
<td>Rash</td>
<td>8 (19)</td>
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<tr>
<td>Diarrhoea</td>
<td>9 (21)</td>
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<tr>
<td>Abdominal pain</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Auditive complaints *</td>
<td>5 (12)</td>
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<tr>
<td>Itching</td>
<td>2 (5)</td>
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<tr>
<td>Palpitations</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
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</table>

PDE= protocol defined exacerbation (*) self-reported mild hearing loss / tinnitus. All data are expressed in No (%) unless otherwise stated.
1. Mann Whitney U test
2. Fisher’s exact test
Discussion

We found a significant difference in exacerbation frequency – our primary endpoint – after one year among 83 adult patients who were randomly assigned to either azithromycin or placebo.

Azithromycin was superior to placebo with respect to lung function (FEV₁ and FVC), disease symptoms and QoL measurements. Exacerbation frequency is considered as one of the most important causes of reduced QoL in non-CF bronchiectasis patients. The current study is the first to evaluate the effect of macrolide maintenance treatment during a full year, thereby reducing seasonal influences on exacerbation frequency and wellbeing. Testing for macrolide resistance was done in most of the sputum pathogens, and this provides important additional information to earlier reports in this field, particularly because the emergence of resistant organisms was not mirrored by loss of efficacy in the subsequent months.

A recently published trial in non-CF bronchiectasis (the ‘EMBRACE’ trial), found a similar significant reduction in exacerbation frequency with 6 months of macrolide treatment. Lung functional improvement and better QoL was not maintained during the 6 months after the intervention concluded. In contrast to the EMBRACE investigators, who found a small but significant reduction of the already low baseline CRP values, CRP values in our study did not change significantly, probably because of lack of power for this secondary endpoint.

Analysis of our secondary endpoints demonstrated a modest but statistically significant improvement of FEV₁ in the azithromycin group as compared to placebo. Apart from Tsang et al., who found improvement in FEV₁ in children, no other study showed functional improvement with macrolide therapy. HRCT-scans in bronchiectasis do not exclusively show dilated bronchi, but also signs of infection like mucus plugging, consolidation and tree-in-bud sign, potentially resulting in air flow limitation and air trapping. Improvement in pulmonary function may eventually impact survival as lung function impairment has been identified as an independent risk factor for mortality in bronchiectasis.

Most macrolides are active against gram-positive organisms and some anaerobes but have limited gram-negative activity. Saiman et al. failed to demonstrate a positive effect on lung function in their trial of azithromycin (250-500 mg three times weekly, 24 weeks vs. placebo) in 260 Pseudomonas-free children with CF and mild lung disease. The positive effect of macrolide treatment in CF has therefore been attributed to an inhibitory effect on Pseudomonas, rather than to an anti-inflammatory effect.

Only around 10% of the patients in the present study were infected by *P. aeruginosa* and colonization rates with *P. aeruginosa* did not importantly change during treatment, pointing towards a favorable effect of macrolide therapy apart from its proposed anti-pseudomonal effect in non-CF bronchiectasis.

Although absolute numbers of sputum pathogens were importantly lower in the azithromycin group, susceptibility testing showed 88% (53 out of 60) macrolide resistance in pathogens from these patients, as compared to 26% (29 out of 112) in the placebo group. A similar trial of macrolides in COPD patients, in which 30% of the pathogens were not available for susceptibility testing, found 81% of macrolide resistance in the azithromycin group as compared to 41% in the placebo group, the latter percentage being lower in our group, due to a lower local baseline rate of macrolide resistance. Other evidence on induction of macrolide resistance comes from CF-studies which report resistance rates up to 100% associated with long-term macrolide treatment. Emergence of macrolide-resistance however, was never linked to pulmonary function decline. Since numerous alternative antimicrobial agents are available to treat airway pathogens and since azithromycin is not considered first choice in patients with exacerbations of non-CF bronchiectasis, macrolide resistance might not necessarily be deleterious in this patient group.

Patients in the azithromycin group reported more gastro-intestinal adverse effects – comparable to other trials of macrolide maintenance therapy- but none were serious and never a reason for treatment discontinuation. In the trial of macrolides in COPD-patients a slight increase of hearing decrements with audiometry was detected. Using a post-study questionnaire, which is less sensitive - a limitation of our study - we could not detect hearing loss. Our study has other limitations. First, our hypothesis – long term macrolide treatment is effective in reducing infectious exacerbations- was tested one-sided. This appeared legitimate in the light of positive treatment results with minimal adverse effects in earlier trials. By choosing this approach we minimized the number of participants and, by
doing so, made efficient use of our resources. Furthermore, this study was not powered for
toxicity.

Second, the incidence of infectious exacerbations in the placebo group was substantially
lower during treatment as compared to the year before study entry (median 2 vs 5). Apart
from a placebo effect, we believe that there could be two possible study-related factors
that might have contributed. First of all, during the trial period patients were encouraged to
report directly to their pulmonary physician in case of an increase of symptoms rather than
visiting their general practitioner. One could argue that a pulmonary specialist would be less
inclined to treat relatively mild symptoms with antibiotics, however we did not screen for
this effect in the current trial. Moreover, since patients had to produce 3-monthly sputum
samples during the trial period, current information about airway pathogens was readily
available when patients presented with an exacerbation. Culture-guided therapy might
have prolonged the time until the next exacerbation.

Third, we did not routinely screen for mycobacterial infection at baseline or exclude patients
with evidence of a non-tuberculous mycobacterial (NTM) infection. Clinical improvement in
participants with NTM infection might therefore be the result of direct anti-mycobacterial
action of macrolides. However, since standard treatment for NTM infection in the
participating hospitals included macrolide treatment and recent use of macrolides was an
exclusion criterion, these patients were not expected to be eligible for randomization. In
addition, sputum cultures obtained at baseline did not yield NTM.

Finally, we did not undertake ECG recording before administering study medication.
Considering the results of a recent cohort study reporting an increased risk of
cardiovascular death during azithromycin use, especially in patients in the highest decile of
risk for cardiovascular disorders, we might have done so in participants at risk (a marginal
percentage of our participants) 35. Neither our study, nor other clinical trials on macrolide
treatment demonstrated an increased risk of death of cardiovascular events 15,29,36.

We conclude that macrolide maintenance therapy was effective in reducing exacerbations
in non-CF bronchiectasis. In this trial, azithromycin-treatment resulted in improved lung
function and better quality of life but involved an increase in gastro-intestinal adverse
effects and high rates of macrolide resistance.

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