Effect of Azithromycin Maintenance Treatment on Infectious Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis

The BAT Randomized Controlled Trial

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Background Bronchiectasis is radiographically characterized by pathologic dilation 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 process may lead to respiratory failure and the need for lung transplantation or to 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 influence on quality of life.1

Macrolide antibiotics have been shown beneficial in cystic fibrosis (CF) and diffuse panbronchiolitis, and earlier findings also suggest a benefit in non-CF bronchiectasis.2 Importantly, macrolide antibiotics have been shown beneficial in cystic fibrosis (CF) and diffuse panbronchiolitis, 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 The BAT (Bronchiectasis and Long-term Azithromycin Treatment) study, a randomized, double-blind, placebo-controlled trial conducted between April 2008 and September 2010 in 14 hospitals in the Netherlands among 83 outpatient with non-CF bronchiectasis and 3 or more lower respiratory tract infections in the preceding year.

Interventions Azithromycin (250 mg daily) or placebo for 12 months.

Main Outcome Measures Number of infectious exacerbations during 12 months of treatment. Secondary end points included lung function, sputum bacteriology, inflammatory markers, adverse effects, symptom scores, and quality of life.

Results Forty-three participants (52%) received azithromycin and 40 (48%) received placebo and were included in the modified intention-to-treat analysis. At end of study, the median number of exacerbations in the azithromycin group was 0 (interquartile range [IQR], 0-1), compared with 2 (IQR, 1-3) in the placebo group (P < .001). Thirty-two (80%) placebotreated vs 20 (46%) azithromycin-treated individuals had at least 1 exacerbation (hazard ratio, 0.29 [95% CI, 0.16-0.51]). In a mixed-model analysis, change in forced expiratory volume in the first second of expiration (percent of predicted) over time differed between groups (F1,78.8 = 4.085, P = .047), with an increase of 1.03% per 3 months in the azithromycin group and a decrease of 0.10% per 3 months in the placebo group. Gastrointestinal adverse effects occurred in 40% of patients in the azithromycin group and in 5% in the placebo group (relative risk, 7.44 [95% CI, 0.97-56.88] for abdominal pain and 8.36 [95% 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, compared with 26% in the placebo group.

Conclusions and Relevance 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. This could result in better quality of life and might influence survival, although effects on antibiotic resistance need to be considered.

Trial Registration clinicaltrials.gov Identifier: NCT00415350

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See also pp 1260 and 1295.

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Efficacy of long-term low-dose macrolide treatment in non-CF bronchiectasis had first been studied in small, mostly nonrandomized studies, showing a positive effect on exacerbation frequency, sputum volume, and inflammatory markers. Recently, Wong et al included 141 patients with non-CF bronchiectasis who received 6 months of either azithromycin (500 mg [3 times weekly]) or placebo. We initiated a multicenter trial to investigate whether 1 year of long-term low-dose macrolide treatment added to standard therapy is effective in reducing exacerbation frequency in patients with non-CF bronchiectasis.

**METHODS**

**Study Design**

The BAT (Bronchiectasis and Long-term Azithromycin Treatment) trial was a multicenter, double-blind, placebo-controlled, parallel-group study with equal randomization (1:1), conducted in 14 hospitals in the Netherlands 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 guidelines, the International Conference on Harmonization guidelines, and the most recent version of the Declaration of Helsinki. The study adhered to the CONSORT (Consolidated Standards for Reporting of Randomized Controlled Trials) guidelines.

**Participants**

Patients who met the inclusion criteria were 18 years or older and had non-CF bronchiectasis diagnosed by plain bronchography or high-resolution computed tomography. All patients had had a minimum of 3 lower respiratory tract infections (LRTIs) treated with oral or intravenous antibiotics in the preceding year and had at least 1 sputum culture yielding 1 or more bacterial respiratory pathogens in the year prior to study entry. Patients were excluded if they received prolonged (>4 weeks) macrolide therapy during the previous 3 months, oral or intravenous courses of corticosteroids within 30 days of screening, or any antimicrobial treatment for an LRTI in the last 2 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 childbearing potential avoiding contraceptives, as well as lactating women; and patients with liver disease or with elevated transaminase levels (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels equal to or greater than the upper limit of normal) were also excluded from the study.

**Setting**

Patients were recruited from outpatient clinics at each of the 14 study sites by their pulmonary physician or the investigator. After patients had provided written informed consent, their medical histories were reviewed and eligible patients were randomized.

**Interventions**

Following randomization, patients were observed for clinical stability for 2 weeks, after which they received either oral azithromycin (250 mg once per day) or placebo for the subsequent 52 weeks. Because of lack of a standard treatment regimen, the 250-mg regimen was chosen to increase patient adherence by daily administration and to minimize adverse effects by choosing a low daily dosage. Adherence was monitored by investigator count of empty blisters of study medication at each study visit.

**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 in advance of performing the primary outcome analysis to omit the small number of events not treated with antibiotics in the analysis of our primary end point.

Two types of exacerbations were included in the primary end point: a protocol-defined exacerbation (PDE) and a non-PDE. An exacerbation was considered a PDE when at least 4 of the following 9 symptoms, signs, or findings were present: (1) change in sputum production (consistency, color, volume, or hemoptysis); (2) increased dyspnea (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) forced expiratory volume in the first second of expiration (FEV₁) or forced vital capacity (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 non-PDE was noted when a patient had fewer than 4 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 through 6) applied to that particular exacerbation. Findings 7 through 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 telephone or fax. At every follow-up visit, patients were specifically asked about exacerbations in the past 3 months. At end of study, a member of the research team visited each participant in the respective hospitals. At these visits, the researcher had full access to the patient’s medical files and double-checked these for reports of infectious exacerbations, courses of antibiotics, or both.

In the case of an infectious exacerbation, the choice of antibiotic regi-
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men was left to the discretion of the attending physician, who was generally not a member of the trial team and who was 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 end points included lung function, serum C-reactive protein (CRP) level, white blood cell (WBC) count, microbiological evaluation, lower respiratory tract symptoms, health-related quality of life (QOL), and adverse effects.

After randomization and a 2-week run-in period, patients underwent follow-up every 3 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, available at http://www.jama.com). Laboratory tests included measurement of serum CRP level, WBC count, and levels of AST and ALT. 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 (eMethods).

Symptoms were measured using the lower respiratory tract infection visual analog scale (LRTI-VAS), a symptom score specifically designed to investigate common symptoms in patients with bronchiectasis (eMethods). This scale consists of a set of horizontal lines with 2 anchor points, one at each extreme, each line representing a different symptom. Each symptom is scored from 1 to 10, the patients being unaware of the numbers. Higher scores indicate more severe symptoms. Five symptom domains were scored: dyspnea, fatigue, cough, chest pain, and sputum color. Separate scores were calculated for each symptom, with a total score consisting of all symptom scores added.

The St George’s Respiratory Questionnaire (SGRQ)—a condition-specific questionnaire—was used to measure health-related QOL. Its 76 items are partitioned into 3 sections (symptoms, activity, impact), which are scored separately and can be added to provide a total score ranging from 0 to 100, with 0 indicating no impairment of QOL. 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 patients with bronchiectasis.

Diary cards with weekly reports of symptoms, courses of antibiotics, and adverse effects (specifically addressing gastrointestinal, 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 1 year of treatment with placebo or azithromycin, patients underwent a 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 were used.

Randomization and Masking
At 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, feel, and taste.

Placebo and azithromycin tablets were provided in identical, individually numbered boxes, each box containing a year’s supply of study medication for 1 participant. Numbers on the boxes matched a treatment allocation, in accordance with a computer-generated allocation sequence that 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 a 33% or greater reduction of the number of exacerbations per patient, decreasing the yearly number of exacerbations per patient from 3 to 2. In 3 small trials, exacerbations were reduced from 3 to 10 per year to 1 to 5 per year during azithromycin therapy. In a study with 24 adult patients with non-CF bronchiectasis, erythromycin reduced median exacerbations from 4 (range, 2-11) to 2 (range, 0-8) per year. Azithromycin in patients with CF reduced exacerbations from 3 to 4 per year to 1.5 to 1.6 per year. These limited available data, combined with our clinical experience in patients with non-CF bronchiectasis, led us to assume that azithromycin would reduce the number of exacerbations by at least one-third.

We calculated that a sample size of 36 participants in each group was required to detect this reduction with a 1-sided significance level of P = .05 and a power of 80%, and we planned to include 90 patients, assuming 20% dropout. One-sided testing was considered appropriate in view of the favorable results of this treatment modality in previous, smaller trials.

Statistical Methods
Statistical analysis was performed on data from the modified intention-to-treat population, defined as all randomized participants who received at least 1 dose of study drug. Patients who were randomized but afterwards appeared not to fulfill inclusion 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 normally distributed and with a Mann-Whitney U test if not normally distributed. There were no patients with missing information on exacerbations during intervention. Time to first exacerbation during the treatment period, as well as during 90 days of run-out, was assessed using Cox proportional hazards regression and re-
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Figure 1. Study Flow

89 Randomized

- 54 Refused to participate
- 2 Immobility
- 2 Participating in another trial

1 Discontinued intervention (adverse effects)

- 1 Infectious exacerbation during run-in
- 1 Withdraw consent

39 Completed 1-year study and entered run-out (≥12 wk) followed by data collection

40 Included in primary analysis

2 Excluded (did not receive ≥1 dose of azithromycin)

42 Completed 1-year study and entered run-out (≥12 wk) followed by data collection

- 3 exacerbations

44 Randomized to receive placebo and entered 2-wk run-in

- 4 Diagnosed with CVID during run-in
- 1 Infectious exacerbation during run-in
- 1 ≥3 exacerbations
- 1 Withdraw consent

45 Randomized to receive azithromycin and entered 2-wk run-in

- 1 Infectious exacerbation during run-in
- 1 Withdraw consent

360 Patients assessed for eligibility

271 Excluded
- 213 Did not meet inclusion criteria
- 88 <3 infectious exacerbations
- 48 No sputum pathogens
- 38 No proven bronchiectasis
- 23 Current macrolide maintenance therapy
- 6 Macrolide intolerance
- 5 No clinical stability prior to run-in
- 4 Pregnant or lactating
- 1 Liver disease
- 54 Refused to participate
- 4 Other

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A total of 117 exacerbations (100 PDE, 17 non-PDE) treated with antibiotics were reported during 1 year of treatment, 78 of which occurred in the placebo group. During the treatment period, the median number of exacerbations in the azithromycin group was 0 (interquartile range [IQR], 0-1), compared with 2 (IQR, 1-3) in the placebo group (P < .001 by Mann-Whitney U test) (TABLE 2). Of the 40 participants receiving placebo, 32 (80%) had at least 1 exacerbation during the study period. In the 43 participants receiving azithromycin, 20 (46.5%) had had at least 1 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 was 3.0.

Time to a first exacerbation in a post hoc analysis differed, with a hazard ratio of 0.29 (95% CI, 0.16-0.51) for participants receiving azithromycin compared with placebo (FIGURE 2A). Time until the first exacerbation did not differ in the run-out period (hazard ratio, 0.56 [95% CI, 0.26-1.19]) (Figure 2B).
Lung Function
Change in percent of predicted FEV₁ over time was different for patients receiving placebo compared with azithromycin ($F_{1,78.8} = 4.085, P = .047$). In patients receiving azithromycin, the percent of predicted FEV₁ increased 1.03 per 3 months (intervals of visits). In patients receiving placebo, percent of predicted FEV₁ decreased 0.10 per 3 months.

Change in percent of predicted FVC over time was different for patients receiving placebo compared with azithromycin ($F_{1,78.6} = 5.9, P = .02$). In patients receiving azithromycin, percent of predicted FVC increased 1.33 per 3 months. In patients receiving placebo, percent of predicted FVC decreased 0.30 per 3 months. Details of the mixed-model analysis are provided in the eResults.

Inflammatory Markers
Change in serum CRP levels and WBC count during the study period was not significantly different between treatment groups.

Microbiology
A total of 437 sputum samples were cultured for microbiology, which yielded 1 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 *Pseudomonas aeruginosa* did not differ between treatment groups or between start and end of study (Table 2).

*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Haemophilus parainfluenzae* were most frequently encountered, together comprising 87% of the total number of pathogens. Seventy-five percent of these pathogens were tested for macrolide resistance.

At baseline, resistance patterns were comparable between groups (35% macrolide resistance in 8 patients in the azithromycin group vs 27.5% in 9 patients in the placebo group; $P = .75$). During treatment, 53 of 60 pathogens

### Table 1. Baseline Patient Characteristics<sup>a</sup>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Azithromycin (n = 43)</th>
<th>Placebo (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>59.9 (12.3)</td>
<td>64.6 (9.1)</td>
</tr>
<tr>
<td>Women</td>
<td>25 (63)</td>
<td>28 (65)</td>
</tr>
<tr>
<td>No. of exacerbations in year before study entry, median (IQR)</td>
<td>4.0 (3-9)</td>
<td>5.0 (3-12)</td>
</tr>
<tr>
<td>Etiology of bronchiectasis&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postinfectious</td>
<td>15 (35)</td>
<td>13 (33)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>12 (28)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Asthma</td>
<td>7 (16)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>3 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Common variable immune disorder</td>
<td>1 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Yellow nail syndrome</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Mechanical obstruction</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>1 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary function, mean (SD), % predicted FEV₁</td>
<td>77.7 (24.4)</td>
<td>82.7 (27.2)</td>
</tr>
<tr>
<td>FVC</td>
<td>91.9 (24.4)</td>
<td>98.5 (23.6)</td>
</tr>
<tr>
<td>CRP, median (IQR), mg/dL</td>
<td>5.0 (2-11.3)</td>
<td>4.5 (2-15.3)</td>
</tr>
<tr>
<td>WBC count, mean (SD), $\times 10^9$ cells/L</td>
<td>8.1 (2.7)</td>
<td>8.1 (3.3)</td>
</tr>
<tr>
<td>SGRQ total score, mean (SD)</td>
<td>40.6 (19.4)</td>
<td>40.2 (20.9)</td>
</tr>
<tr>
<td>LRTI-VAS total score, mean (SD)</td>
<td>17.5 (10)</td>
<td>17.9 (8.0)</td>
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<tr>
<td>Baseline sputum microbiology</td>
<td></td>
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<tr>
<td><em>Haemophilus influenzae</em></td>
<td>13 (30)</td>
<td>9 (23)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>4 (9)</td>
<td>9 (23)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>6 (14)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Hearing impairment previous to study entry&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 (28)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Body mass index&lt;sup&gt;d&lt;/sup&gt;</td>
<td>23.0 (3.4)</td>
<td>24.5 (4.0)</td>
</tr>
<tr>
<td>Abnormalities on auscultation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crackles</td>
<td>20 (47)</td>
<td>11 (28)</td>
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<tr>
<td>Rhonchi</td>
<td>8 (19)</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>7 (16)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Dullness</td>
<td>0</td>
<td>1 (3)</td>
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<tr>
<td>Smoking status</td>
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<td></td>
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<tr>
<td>Current</td>
<td>1 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Former</td>
<td>19 (44)</td>
<td>17 (43)</td>
</tr>
<tr>
<td>Treatment previous to study entry&lt;sup&gt;e&lt;/sup&gt;</td>
<td>38 (88.4)</td>
<td>32 (80)</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>34 (79)</td>
<td>30 (75)</td>
</tr>
<tr>
<td>Inhaled antibiotics</td>
<td>4 (9)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Long-term oral antibiotic treatment</td>
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<td>2 (5)</td>
</tr>
<tr>
<td>Airway clearance techniques&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>11 (26)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Weekly</td>
<td>3 (7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>During exacerbation</td>
<td>4 (9)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; FEV₁, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; IQR, interquartile range; LRTI-VAS, lower respiratory tract infection–visual analog score; SGRQ, St George’s Respiratory Questionnaire; WBC, white blood cell.

<sup>a</sup>No between-group differences were statistically significant.

<sup>b</sup>As described by the treating pulmonary physician.

<sup>c</sup>Patient reported.

<sup>d</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>e</sup>Treatment started before study entry and continued during the study period.

<sup>f</sup>Any technique taught by a physiotherapist and performed by the patient to evacuate sputum.

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(88%) tested for sensitivity in 20 patients in the azithromycin group became macrolide resistant, compared with 29 of 112 pathogens (26%) in 22 patients in the placebo group ($P < .001$ by $t$ test) (Table 1 and eResults).

**QOL and Patient-Reported Symptoms**

Quality of life as measured by the SGRQ showed a larger decrease of the total score (indicating better QOL) in patients receiving azithromycin at the end of treatment compared with patients receiving placebo ($P = .046$). Quality of life assessed by the SGRQ was measured at the start of intervention and after 6 and 12 months. In patients receiving azithromycin, SGRQ total score decreased $-6.09$ per 6 months. This means that in the mixed model patients had an average decrease in SGRQ score of $2 \times 6.09 = 12.18$ after 1 year of treatment. In patients receiving 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 1 year, 28 patients (64%) in the azithromycin group had an improvement of 4 units, as compared with 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 fewer symptoms) in patients receiving azithromycin at the end of treatment as compared with patients receiving placebo ($P = .047$). In patients receiving azithromycin, total LRTI-VAS score decreased $1.11$ per 3 months. This means that in the mixed model patients had a mean decrease of total LRTI-VAS score of 4 (follow-up visits until end of treatment) $\times 1.11 = 4.44$ after 1 year of treatment. In patients receiving placebo, LRTI-VAS total score decreased 0.056 per 3 months (more detailed results of the mixed-model analysis are reported in the eResults).

**Safety**

Among the adverse effects reported, only 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%); 1 patient in the placebo group (2.5%) developed a severe rash and was subsequently diagnosed with psoriasis; and 1 patient in the azithromycin group (2.3%) reported progressive fatigue, which did not resolve after discontinu-
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Figure 2. Proportion of Patients Remaining Exacerbation Free

A Recently published trial of non-CF bronchiectasis (the EMBRACE trial) found a similar significant reduction in exacerbation frequency with 6 months of macrolide treatment.13 Lung functional improvement and better QOL was not maintained during the 6 months after the intervention concluded. In contrast to the EMBRACE study, which 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 end point.

To our knowledge, the current study is the first to evaluate the effect of azithromycin maintenance treatment during a full year, thereby reducing seasonal influences on exacerbation frequency and well-being. Most of the sputum pathogens were tested for macrolide resistance; 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.

Analysis of our secondary end points demonstrated a modest but statistically significant improvement of FEV1 in the azithromycin group compared with the placebo group. Apart from the study by Tsang et al,13 which found improvement in FEV1 in children, no other study showed functional improvement with macrolide therapy. High-resolution computed tomography scans in patients with bronchiectasis do not exclusively show dilated bronchi but also signs of infection, such as mucus plugging, consolidation, and tree-in-bud sign, potentially resulting in airflow limitation and air trapping. Improvement in pulmonary function may eventually affect survival, because impaired lung function has been identified as an independent risk factor for mortality in patients with bronchiectasis.27

Most macrolides are active against gram-positive organisms and some anaerobes but have limited gram-negative activity. The study by Saiman et al28 failed to demonstrate a positive effect on lung function in their trial of azithromycin (250-500 mg 3 times weekly, 24 weeks vs placebo) in 260 Pseudomonas-free children with CF and mild lung disease. The positive effect of macrolide treatment in patients with CF has therefore been attributed to an inhibitory effect on Pseudomonas, rather than to an anti-inflammatory effect.

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

Although absolute numbers of sputum pathogens were lower in the azithromycin group, susceptibility testing showed 88% (53/60) macrolide resistance in pathogens from these patients, compared with 26% (29/112) in the placebo group. A similar trial of macrolides in patients with chronic obstructive pulmonary disease, in which 30% of the pathogens were not available for susceptibility testing, found 81% macrolide resistance in the azithromycin group compared with 41% in the placebo group, the latter percentage being lower in our group because of a lower local baseline rate of macrolide resistance.**29**

Other evidence on induction of macrolide resistance comes from CF studies that report resistance rates up to 100% associated with long-term macrolide treatment.**28** Emergence of macrolide resistance, however, was never linked to decline in pulmonary function.**28,30-34** Because numerous alternative antimicrobial agents are available to treat airway pathogens and because 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. However, an important risk of induction of macrolide resistance is linked to an increase of macrolide-resistant microorganisms (pathogens and commensals alike) in the community. Because macrolides are often recommended as first-line agents for the treatment of community-acquired pneumonia, macrolide resistance could be a potential cause for treatment failure in patients with community-acquired pneumonia. Although the exceptional tissue penetration of macrolides causes differences in both in vivo and in vitro resistance results—macrolides have been shown to be effective against microorganisms with low-level macrolide resistance (minimum inhibitory concentration, 8-16 μg/mL)—the increasing prevalence of macrolide resistance in “innocent bystander” organisms is a matter of concern. Macrolide maintenance therapy should therefore be prescribed exclusively to patients with bronchiectasis who experience at least 3 exacerbations annually.

Patients in the azithromycin group reported more gastrointestinal adverse effects—comparable with other trials of macrolide maintenance therapy—but none were serious and were never a reason for treatment discontinuation.**13**

In the trial of macrolides in patients with chronic obstructive pulmonary disease, a slight increase of hearing decrements with audiometry was detected. Using a poststudy questionnaire, which is less sensitive—a limitation of our study—we could not detect hearing loss.**20**

Our study has other limitations. First, our hypothesis—long-term macrolide treatment is effective in reducing infectious exacerbations—was tested 1-sided. This appeared legitimate, in light of positive treatment results with minimal adverse effects in earlier trials.**4,7,9-14** By choosing this approach we minimized the number of participants and, in 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 compared with the year before study entry (median, 2 vs 5). Apart from a placebo effect, we believe that 2 possible study-related factors might have contributed. First, 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, because patients were required to produce sputum samples every 3 months 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 antimycobacterial action of macrolides. However, because 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 indicate NTM infection.

Fourth, we did not undertake electrocardiographic 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).**12** Neither our study nor other clinical trials of macrolide treatment demonstrated an increased risk of death from cardiovascular events.**15,20,36**

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

**Author Contributions:** Dr Altenburg and Boenema had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Critical revision of the manuscript for important intellectual content: C. K. P. van der Ploeg, MSc (Medical Center Alkmaar/Inholland University, Alkmaar), for statistical help and advice. We also thank all pulmonary physicians and the outpatient department staff of the participating hospitals: J. M. W. van Haarst, MD, PhD, and P. J. H. Janssen, MD (Tergooi Hospitals, Hilversum), I. van der Lee, MD, PhD (Spaane Hospital, Hoofddorp), F. Brijker, MD, PhD (Diakonessen Hospital, Utrecht), B. Hajian, MD, PhD (Amsterdam Medical Centre, Amsterdam, the Netherlands), J. W. K. van den Berg, MD, PhD (Isala Clinics, Zwolle), W. J. A. Wijnands, MD, PhD (Deventer Hospital, Deventer), B. T. J. van den Berg, MD, PhD (St Lucas Andreas Hospital, Amsterdam), M. H. E. Reijers, MD, PhD (University Lung Centre Dekkerwald, Groesbeek), M. M. van der Eerden, MD, PhD (Erasmus Medical Centre, Rotterdam), and E. F. G. Kapteijns, MD (Rode Kruis Hospital, Beverwijk). These collaborators did not receive any compensation for their contributions.

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