Effect of Long-term, Low-Dose Erythromycin on Pulmonary Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis

The BLESS Randomized Controlled Trial

**Importance** Macrolide antibiotics such as erythromycin may improve clinical outcomes in non–cystic fibrosis (CF) bronchiectasis, although associated risks of macrolide resistance are poorly defined.

**Objective** To evaluate the clinical efficacy and antimicrobial resistance cost of low-dose erythromycin given for 12 months to patients with non–CF bronchiectasis with a history of frequent pulmonary exacerbations.

**Design, Setting, and Participants** Twelve-month, randomized (1:1), double-blind, placebo-controlled trial of erythromycin in currently nonsmoking, adult patients with non–CF bronchiectasis with a history of 2 or more infective exacerbations in the preceding year. This Australian study was undertaken between October 2008 and December 2011 in a university teaching hospital, with participants also recruited via respiratory physicians at other centers and from public radio advertisements.

**Interventions** Twice-daily erythromycin ethylsuccinate (400 mg) or matching placebo.

**Main Outcome Measures** The primary outcome was the annualized mean rate of protocol-defined pulmonary exacerbations (PDPEs) per patient. Secondary outcomes included macrolide resistance in commensal oropharyngeal streptococci and lung function.

**Results** Six-hundred seventy-nine patients were screened, 117 were randomized (58 placebo; 59 erythromycin), and 107 (91.5%) completed the study. Erythromycin significantly reduced PDPEs both overall (mean, 1.29 [95% CI, 0.93-1.65] vs 1.97 [95% CI, 1.45-2.48] per patient per year; incidence rate ratio [IRR], 0.57 [95% CI, 0.42-0.77]; *P* = .003), and in the prespecified subgroup with baseline macrolide resistance in commensal oropharyngeal streptococci and lung function.

**Conclusion and Relevance** Among patients with non–CF bronchiectasis, the 12-month use of erythromycin compared with placebo resulted in a modest decrease in the rate of pulmonary exacerbations and an increased rate of macrolide resistance.
resistance development. Erythromycin offers macrolide-related clinical benefits with a lower risk of induction of macrolide resistance than azithromycin.\(^8\) It is also substantially cheaper than azithromycin (in Australia, annual cost approximately US $190 for 400 mg twice daily\(^\text{14}\) vs US $1200 for azithromycin, 500 mg, 3 times weekly\(^\text{13}\)) and is widely available even in countries outside the developed world.

The Bronchiectasis and Low-dose Erythromycin Study (BLESS) tested the hypothesis that low-dose erythromycin would reduce pulmonary exacerbations in non–CF bronchiectasis patients with a history of frequent exacerbations. Additionally, the bacterial resistance caused by this therapy, arguably the primary risk associated with long-term macrolide therapy, was precisely quantified in commensal bacterial flora.

**METHODS**

Adult patients aged 20 to 85 years were eligible if they had bronchiectasis documented by high-resolution computed tomographic scan, at least 2 separate pulmonary exacerbations requiring supplemental systemic antibiotic therapy in the preceding 12 months, and daily sputum production. Participants were required to have been clinically stable for at least 4 weeks prior to enrollment (defined as no symptoms of exacerbation, no requirement for supplemental antibiotic therapy, and forced expiratory volume in the first second of expiration [FEV\(_1\)] within 10% of best recently recorded value where available). Exclusion criteria included CF, current mycobacterial disease or bronchopulmonary aspergillosis, any reversible cause for exacerbations, maintenance oral antibiotic prophylaxis, prior macrolide use except short-term, changes to medications in the preceding 4 weeks, cigarette smoking within 6 months, and medications or comorbidities with the potential for important interactions with erythromycin. All participants required negative results from sputum mycobacterial cultures prior to randomization. The study was approved by the Mater Health Service human research ethics committee, and all participants provided written, informed consent.

**Study Design and Procedures**

This was a randomized, double-blind, placebo-controlled study of oral erythromycin ethylsuccinate, 400 mg (equivalent to 250-mg erythromycin base), given twice daily for 48 weeks, followed by a 4-week washout period. The study was undertaken at an Australian university teaching hospital through the respiratory medicine department, which is also a regional adult CF center. In addition to recruiting individuals seen at the center, we recruited participants through respiratory physicians at other centers and from 2 regional public radio advertisement campaigns. Erythromycin and placebo (spray-dried lactose/magnesium stearate) tablets were manufactured and supplied by Alphapharm and were identical in shape, appearance, and taste.

Computer-generated randomization sequences, blocked in random groups of 2, 4, and 8 and stratified for presence of sputum *Pseudomonas aeruginosa* at screening, were held by the Department of Pharmacy. The independent trial pharmacist dispensed blinded study drug according to the randomization sequence. Trial participants, trial supervisors, and all staff directly involved in patient care were unaware of treatment assignment at all times. All study measurements, data collection, and data entry were completed before treatment codes were broken.

Participants visited the center for examinations 3 times in the first 8 weeks and a total of 8 times over 40 weeks (during this period, they were also contacted by telephone every 4 weeks, between visits); each participant had a final follow-up visit at week 52 after the 4-week washout period (eFigure 1). At office visits and in telephone interviews, we documented details regarding symptoms of exacerbation. At all examinations, participants provided a 24-hour sputum collection and completed spirometry and questionnaires about symptoms (Leicester cough questionnaire) and quality of life (St George’s Respiratory Questionnaire [SGRQ]). A number of other assessments were performed at different time points across the study, including 6-minute walk test, electrocardiogram, sputum collection for microbiology and inflammatory cell counts, venesection for hematology, clinical chemistry and C-reactive protein measurement, and throat swabs for oropharyngeal streptococcal culture and macrolide sensitivity testing (modified from methods described by Malhotra-Kumar et al.\(^9\) (Details about the visits and all methods appear in the eMethods, available at http://www.jama.com.)

Participants were provided with 24-hour contact details and invited to contact study staff (M.L.M. or D.J.S.) at any time (including after hours) in the event of exacerbation symptoms, to ensure that these symptoms were evaluated prospectively. Participants were directed to ensure that antibiotic prescriptions were provided through the center rather than alternative sources. Criteria for protocol-defined pulmonary exacerbation (PDPE) were adjudicated prospectively by two of us (D.J.S. or M.L.M.). Antibiotic prescriptions were directed by one of us (D.J.S.), provided by study staff, and standardized according to microbiology and antibacterial tolerance. Deteriorations in respiratory symptoms that did not meet criteria for PDPEs were termed non–protocol-defined PEs (non-PDPEs). In these circumstances, participants were advised that they did not require antibiotics and prescriptions were not provided.

**Outcome Measures**

The primary end point was the mean rate of PDPEs per patient per year, analyzed by intention to treat (all randomized participants who contributed data). A PDPE was considered to have occurred when the participant required antibiotic administration for a sustained (>24-hour) increase in spu-
formed, of PDPEs according to the pres-visit by pill counts. A single prespeci-
grams. Adherence was assessed at each

tum volume or purulence accompa-
nied by new deteriorations in at least
2 additional symptoms: sputum vol-
ume, sputum purulence, cough, dys-
pnea, chest pain, or hemoptysis.

Secondary end points included the
rate of all pulmonary events (ie, PDPEs
plus non-PDPEs) for which partici-
pants commenced antibiotics, total days
of antibiotics, change in the propor-
tion of exacerbations in the control group
between placebo and erythromycin with
last-observation-carried-forward (LOCF)
analyses for missing data and, as a sen-
sitivity analysis, multiple imputation of
missing data. All reported results are for
the intention-to-treat population. Mea-
ures of effect are reported with 95% con-
fidence intervals unless otherwise indi-
cated. All analyses were 2-sided, and P
values < .05 were considered signifi-
cant. Statistical analyses were per-
formed using StatsDirect statistical soft-
ware (version 2.7.8).

RESULTS

From October 2008 to December 2011,
679 participants were screened, 562
were excluded, 117 were randomized
(data for all participants included in all
intention-to-treat analyses), and 107
(91.5%) completed the treatment pe-
dium period (FIGURE 1). Attrition was
lower than anticipated and trial recruit-
ment was halted after 98 participants com-
pleted visit 8; at that point, 117 par-
ticipants had undergone randomiza-
tion and commenced the study. Overall
adherence measured by pill counts was
96.5% for placebo and 95.6% for eryth-
romycin. Baseline demographic data are
shown in TABLE 1. Etiologies were id-
idiopathic (n=65, 55.6%), postinfec-
tious (n=34, 29.1%), pink disease
(n=11, 9.4%), ciliary dysfunction (n=3,
2.6%), prior bronchopulmonary asper-
gillosis (n=3, 2.6%), and rheumatoid
arthritis (n=1, 0.8%). Four other par-
ticipants also had coexistent rheuma-
toid arthritis.

Protocol-Defined Pulmonary
Exacerbations

Erythromycin significantly reduced
PDPEs (76 for erythromycin group vs

From October 2008 to December 2011, 679 participants were screened, 562 were excluded, 117 were randomized (data for all participants included in all intention-to-treat analyses), and 107 (91.5%) completed the treatment period (FIGURE 1). Attrition was lower than anticipated and trial recruitment was halted after 98 participants completed visit 8; at that point, 117 participants had undergone randomization and commenced the study. Overall adherence measured by pill counts was 96.5% for placebo and 95.6% for erythromycin. Baseline demographic data are shown in TABLE 1. Etiologies were idiopathic (n=65, 55.6%), postinfectious (n=34, 29.1%), pink disease (n=11, 9.4%), ciliary dysfunction (n=3, 2.6%), prior bronchopulmonary aspergillosis (n=3, 2.6%), and rheumatoid arthritis (n=1, 0.8%). Four other participants also had coexistent rheumatoid arthritis.

Protocol-Defined Pulmonary
Exacerbations

Erythromycin significantly reduced
PDPEs (76 for erythromycin group vs

Data Analysis

Assuming a baseline (SD) annual rate
of exacerbations in the control group
of 2.9 (1.2), 98 participants gave 90% power at the 5% significance level to
show a 28% reduction in exacerbation
rate with erythromycin, a much more
conservative estimate of efficacy than
the 50% reduction seen in our uncon-
trolled pilot data.17 Assuming 20% attri-
tion, the required sample size was in-
creased to 118.

A Poisson regression model was used
to analyze the primary outcome mea-
sure, evaluating both events and expo-
sure (person-time), employing a quasi-
likelihood factor (with overdispersion
correction), and incorporating the fol-
lowing covariables: treatment assign-
ment, age, sex, smoking history, and
presence of P aeruginosa at baseline. Sec-
ondary outcomes (including the sub-
group analysis) were assessed using dif-
ferent measures according to the
outcome and data distribution but in-
cluded analysis of covariance (using base-
line values as the covariate and pro-
vided assumptions of normality and
linearity were met), nonparametric tests,
and Fisher exact test. Assessment of in-
teraction was performed by testing the
heterogeneity of treatment effects be-
tween subgroups using the method de-
scribed by Matthews and Altman.18 All
noncumulative end points were ana-
alyzed as the change between weeks 0
and 48, comparing difference in change be-
tween placebo and erythromycin with
last-observation-carried-forward (LOCF)
analyses for missing data and, as a sen-
sitivity analysis, multiple imputation of
missing data. All reported results are for
the intention-to-treat population. Mea-
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cated. All analyses were 2-sided, and P
values < .05 were considered signifi-
cant. Statistical analyses were per-
formed using StatsDirect statistical soft-
ware (version 2.7.8).
rates is in eTable 1.)

In the eResults, and a summary of event
difference, 0.88 [95% CI, 0.46-0.74]; P = .003 (Figure 2).
The number of patients treated with erythromycin who had 0 PDPEs was 20
(vs 16 for placebo, 20 patients had 1 PDPE (vs 12), 9 had 2 PDPEs (vs 12),
and 10 had more than 2 PDPEs (vs 18).

Prespecified subgroup analysis according
to the presence of sputum
P aeruginosa at baseline (either screen or visit 1) revealed fewer PDPEs in patients
treated with erythromycin (36 PDPEs in 23 erythromycin participants
vs 52 in 18 placebo participants; mean, 1.57 [95% CI, 0.94 to 2.19] vs
2.89 [95% CI, 1.83 to 3.95]; difference, 1.32 [95% CI, 0.19 to 2.46];
P = .02). However, test of interaction was not statistically significant (mean difference,
0.88 [95% CI, -0.41 to 2.17];
P = .18). (Details about exacerbations are in the eResults, and a summary of event
rates is in eTable 1.)

Secondary Outcome Measures

There were 97 non-PDPEs (35 erythromycin vs 62 placebo), and for 33 of
these, participants took antibiotics (13 events in 8 placebo participants, 20 in
10 erythromycin participants). There were significantly fewer total respiratory
events (total PDPEs plus non-PDPEs) in the erythromycin group (111
vs 176 for placebo; mean, 1.88 [95% CI, 1.37-2.39] vs 3.03 [95% CI, 2.47-3.60]
per patient per year; IRR, 0.58 [95% CI, 0.46-0.74]; P < .001). Total
days of antibiotics per patient for PDPEs did not differ significantly (median
erythromycin, 10 days [IQR, 0-24] vs placebo, 15 days [IQR, 0-31]; difference,
5 days [IQR, 0-11]; P = .11). Erythromycin significantly reduced 24-
hour sputum weight (Figure 3) and significantly arrested the decline in
FEV1 percent predicted across the study (Table 2). Post hoc analysis using the
mean of all FEV1 percent-predicted
measurements during the treatment period to reduce variability5 confirmed
this significant effect (eResults). Results
using multiple imputation analysis (eTable 2) were similar to results
using LOCF analysis (Table 2).

Erythromycin did not significantly alter
Leicester cough questionnaire scores
(eFigure 2), SGRQ scores, or percent sputum neutrophils, and no effect was
seen on C-reactive protein level or 6-minute
walk test results (Table 2 and

<table>
<thead>
<tr>
<th>Table 1. Baseline Demographics and Disease Characteristics</th>
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<tbody>
<tr>
<td>Placebo (n = 58)</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
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<tr>
<td>Female sex, No. (%)</td>
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<tr>
<td>FEV1, mean (SD)</td>
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<tr>
<td>Prebronchodilator, L</td>
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<tr>
<td>Postbronchodilator, L</td>
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<tr>
<td>24-hour sputum weight, median (IQR), g</td>
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<tr>
<td>SGRQ total score, mean (SD)</td>
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<tr>
<td>LOQ score, mean (SD)</td>
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<tr>
<td>Sputum neutrophils, median (IQR), %e</td>
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<tr>
<td>Other sputum pathogens at screen, No. (%)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Normal flora</td>
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<tr>
<td>Normal flora</td>
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<tr>
<td>Smoking history, mean (SD), pack-years</td>
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<tr>
<td>Mediated OR</td>
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<tr>
<td>Sputum eosinophils, median (IQR), %e</td>
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<tr>
<td>Comorbidities, No. (%)</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Asthma</td>
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<td>Ischemic heart disease</td>
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<tr>
<td>Cerebrovascular disease</td>
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<tr>
<td>Diabetes mellitus</td>
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</tbody>
</table>

Abbreviations: FEV1, forced expiratory volume in the first second; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, long-acting β-agonists; LOQ, Leicester cough questionnaire; SABA, short-acting β-agonists; SGRQ, St George’s Respiratory Questionnaire.

5 There were no significant between-group differences.
6 Participants were stratified according to a screening visit sputum culturing P aeruginosa (17 in each group); however, 7 additional participants had P aeruginosa cultured at visit 1, prior to commencing trial drug.
6 Lower scores indicate better quality of life.
6 Lower scores indicate worse cough symptoms (range, 3-21).
6 Percentage of total nonsquamous cells.
Erythromycin significantly increased the proportion of macrolide-resistant commensal oropharyngeal streptococci (median change, 27.7% [IQR, 0.04% to 41.1%] vs 0.04% for placebo [IQR, −1.6% to 1.5%]; difference, 25.5% [IQR, 15.0% to 33.7%]; P < .001).

Results of sputum microbiology are described in detail in the eResults and eTables 3 to 6. Briefly, there was no difference between the 2 groups for the emergence of new sputum pathogens at any time after commencing trial medication. However, eradication of sputum pathogens (negative sputum culture in the visit 8 sputum sample, from participants with pathogenic bacteria identified in baseline samples) occurred in more erythromycin-treated participants (17 [30.4%] vs 6 placebo participants [10.9%]; odds ratio, 3.6 [95% CI, 1.3–10.6]; P = .01).

Comparing results at the completion of the 4-week washout period (visit 9) with those at the end of the treatment period (visit 8) did not demonstrate any significant between-group differences for any measure (eResults).

**Adverse Events and Additional Analyses**

There were no deaths and 1 non-PDPE serious adverse event, a placebo participant hospitalized for a respiratory viral infection (without meeting PDPE criteria). Excluding bronchiectasis-related events, 15 (25.9%) placebo and 17 (28.8%) erythromycin participants reported any adverse event. Two participants discontinued study drug due to adverse events: 1 in the placebo group (nausea) and 1 in the erythromycin group (suspected corrected QT interval [QTc] prolongation). This participant had been randomized despite an enrollment QTc of 480 ms and discontinued the study at week 24 with a QTc of 470 ms. Following discontinuation of trial medication (without unblinding), QTc measured 470 ms. There was no difference between placebo and erythromycin for change in the QTc (by Framingham equation) (median, 0 [IQR, −0.01 to 0.01] vs 0 [IQR, −0.01 to 0.01]; 95% CI, −0.01 to 0.01; P = .44). No participant developed new cardiac arrhythmia during the study. Three placebo participants reported nausea; 3 participants (2 placebo, 1 erythromycin) experienced acute sinusitis; and there were single new diagnoses of colorectal carcinoma (erythromycin group), rheumatoid arthritis (erythromycin), and coronary artery disease (placebo).

Exploratory subgroup analyses according to degree of sputum neutrophilia and *Haemophilus influenzae* infection showed no evidence of subgroup benefit. The subgroup with very high baseline pulmonary exacerbation rate (≥5 exacerbations in the preceding year) did show a benefit with erythromycin (P = .01), but the effect was not significantly different than in the subgroup with fewer exacerbations (test of interaction, P = .053).

**COMMENT**

In patients with non-CF bronchiectasis with a history of frequent pulmonary ex-
the rate of PDPEs observed in the placebo group was lower than expected, particularly because more than one-third of study participants reported at least 5 exacerbations per year at baseline. It is likely that many of the exacerbations for which patients ordinarily take antibiotics outside the trial would not meet the criteria for PDPE, and placebo event rates including non-PDPEs were in keeping with anticipated exacerbation rates (mean, 3.3 per year in per-protocol sample).

The mean annualized relative reduction in exacerbation rates with erythromycin (43%) was larger than our powering estimates (28%); however, the absolute mean reduction in exacerbations per patient per year (0.7) was slightly lower than the corresponding assumption (0.8 exacerbations). This is likely to reflect the unadjusted nature of event rates reported (applying the adjusted IRR to the placebo group rates gives an absolute reduction of 0.85) and the lower-than-anticipated rate of PDPEs observed. Subgroup analyses support this latter interpretation, with an absolute reduction in PDPEs of 1.45 seen in those with a history of at least 5 exacerbations in the year preceding study enrollment. Furthermore, the absolute reduction in PDPEs is similar to that seen with azithromycin and greater than reported with azithromycin (0.35) in chronic obstructive pulmonary disease, although somewhat less than the 0.98 reduction recently reported with azithromycin in bronchiectasis. The definition of exacerbation in that study differed from the current study (BLESS required five symptoms rather than two), and an absolute reduction of 1.15 was observed in BLESS using a lower threshold for definition of exacerbation (ie, PDPEs plus non-PDPEs).

Low-dose erythromycin therapy was well tolerated without evidence of adverse events including gastrointestinal intolerance. A small increase in the risk of sudden cardiac death has been reported with daily doses of oral erythromycin at least double that used in BLESS, strongly related to concomitant use of strong inhibitors of cytochrome P-450 3A (CYP3A) enzymes. The current study was not powered to address this issue, although there was no evidence of QTc prolongation or arrhythmogenicity. Ototoxicity was not systematically assessed; however, this complication is uncommon with doses less than 8 times that used in BLESS.

If the lack of significant improvements in SGRQ score is truly indicative of no quality-of-life benefit with erythromycin, then the value of this therapy is questionable. However, we saw consistent, significant benefits on virtually all other important clinical markers. Furthermore, there were trends to improvement in SGRQ scores with erythromycin, and the lack of statistical significance probably reflects a combination of relative lack of sensitivity of the SGRQ in this population and relative underpowering for this end point. The EMBRACE trial also failed to demonstrate significant improvement in SGRQ.

### Table 2. Secondary Outcome Measures

<table>
<thead>
<tr>
<th>Change From Baseline to Visit 8</th>
<th>Placebo (n = 58)</th>
<th>Erythromycin (n = 59)</th>
<th>Treatment Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postbronchodilator FEV1, mean (SD), % predicted</td>
<td>4.0 (6.6)</td>
<td>-1.6 (4.6)</td>
<td>2.2 (0.1 to 4.3)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>-3.36 (-7.88 to 0)</td>
<td>-4.11 (-5.03 to 1.06)</td>
<td></td>
</tr>
<tr>
<td>24-hour sputum weight, median (IQR), g</td>
<td>-1.7 (-8.2 to 2.6)</td>
<td>-5.4 (-16.0 to -1.3)</td>
<td>-4.3 (-7.8 to -1)</td>
</tr>
<tr>
<td>SGRQ total score, mean (SD)</td>
<td>-1.3 (14.5)</td>
<td>-3.9 (10.0)</td>
<td>-2.9 (-7.3 to 1.6)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>-2.8 (-8.8 to 8.4)</td>
<td>-3.7 (-8.5 to 4.2)</td>
<td></td>
</tr>
<tr>
<td>SGRQ symptom score, mean (SD)</td>
<td>-3 (24.3)</td>
<td>-6 (23.5)</td>
<td>-6.3 (-12.6 to 2.1)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.3 (-18.7 to 12.4)</td>
<td>-8.5 (-18.4 to 15.7)</td>
<td></td>
</tr>
<tr>
<td>LCQ score, mean (SD)</td>
<td>0.52 (3.0)</td>
<td>1.16 (3.1)</td>
<td>0.79 (-0.2 to 1.8)</td>
</tr>
<tr>
<td>6-min walk test, median (IQR), m</td>
<td>0 (23 to 25)</td>
<td>2 (12 to 18)</td>
<td>3.55 (-17.6 to 24.7)</td>
</tr>
<tr>
<td>CRP, median (IQR), mg/L</td>
<td>-0.5 (-2.1 to 1.0)</td>
<td>-0.7 (-2.7 to 1.6)</td>
<td>-0.2 (-1.5 to 1.2)</td>
</tr>
<tr>
<td>Sputum neutrophils, median (IQR), %</td>
<td>0.75 (1.2 to 3.5)</td>
<td>-0.8 (-4.8 to 1.0)</td>
<td>-2.1 (-5 to 0)</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; FEV1, forced expiratory volume in the first second; IQR, interquartile range; LCQ, Leicester cough questionnaire; SGRQ, St George’s Respiratory Questionnaire.

1Treatment effect refers to the corrected mean difference or the unadjusted median difference between groups. The statistical methods used to derive the P values and data were analysis of covariance, except for 24-hour sputum weight, CRP, sputum neutrophils, which were all Mann-Whitney U test.

2P = .04.
3Lower scores indicate better quality of life.
4Lower scores indicate worse cough symptoms (range, 3-21).
5Missing baseline values for CRP limited the analysis to 54 erythromycin and 50 placebo participants. Missing data were not imputed for this outcome.
6Neutrophils in sputum as a percentage of total nonsquamous cells. Because of resourcing issues in relation to immediate sputum processing for cell counts, results from paired samples processed within the required time frame were available for only 27 erythromycin participants and 30 placebo participants.

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This study was conducted at a single center. However, the majority of participants screened and randomized were not patients from our own center, instead recruited from other centers directly from community referrals. Screened participants were therefore broadly representative of urban Australian patients with non-CF bronchiectasis, although the large number of participants excluded demonstrates the rigor applied to ensuring that only appropriate patients were randomized. Our study design and results argue strongly against generalizing these results to patients with bronchiectasis more broadly, given potential ecological risks.

Sputum *P aeruginosa* infection has consistently been shown to be associated with poorer outcomes, including more pulmonary exacerbations, accelerated lung function decline, and increased mortality. Hence, the relatively high proportion of participants with baseline *P aeruginosa* airway infection in BLESS predicted a patient population at higher risk for lung function decline. The magnitude of the placebo group FEV₁ decline was identical to that seen in the largest published study in non-CF bronchiectasis to date (using equivalent methodology, 3.4% over 48 weeks in BLESS vs 1.7% over 24 weeks). Erthromycin provided significant protection against this decline across the study, an effect not seen in the recently published azithromycin study. This difference reflects both the higher-risk patient population in BLESS and the substantially longer treatment period. Additionally, the significant lowering of sputum production by erythromycin is likely to have been a key contributor to reduced airways obstruction, and perhaps azithromycin did not demonstrate this same effect, for example, if participants in EMBRACE had lower baseline sputum production. Preservation of lung function is a particularly important tum production. Preservation of lung function is a particularly important concern given the accelerated lung function decline,25 and improving morbidity.

Despite the clinical benefits seen with erythromycin, the increases in resistance in commensal oropharyngeal *streptococci* must curb enthusiasm for its widespread application. There are no comparable results from prior clinical macrolide studies, which have generally investigated macrolide resistance in a limited spectrum of predefined pathogens. A study of azithromycin given to volunteers for 3 days demonstrated a maximal, mean increase in macrolide resistance proportions of 60.4% (95% CI, 53.9%-67%) and peak resistance of greater than 85%; corresponding values from BLESS after 4 weeks of erythromycin were 36.0% (95% CI, 26.7%-45.4%) and 48.5%. The higher rates of macrolide resistance with azithromycin are consistent with prior data linking increases in population *Streptococcus pneumoniae* macrolide resistance rates to increasing consumption of azithromycin, an effect implied by its long half-life, which allows for extended periods of subinhibitory concentrations. In the absence of a direct randomized controlled trial comparison of long-term azithromycin and erythromycin, it is not possible to unequivocally conclude that erythromycin use is preferable because it induces less resistance, although all available data support that interpretation.

The mechanism by which macrolides result in clinical benefits in inflammatory lung diseases remains unknown. A traditional antibiotic mechanism is unlikely against *P aeruginosa*. However, there was evidence of increased bacterial pathogen eradication with erythromycin, and macrolides have shown nonconventional antimicrobial effects, including the demonstration of alterations to *P aeruginosa* morphology and inhibition of adherence to respiratory epithelium with erythromycin exposure in vitro. Additionally, erythromycin significantly reduced sputum production. This may represent direct attenuation of mucus secretion, as has been demonstrated in murine and in vitro studies, although reduced mucus production is probably also a predictable consequence of antibacterial or anti-inflammatory effects.

In conclusion, long-term low-dose erythromycin significantly reduced exacerbations, protected against lung function decline, reduced sputum production, and significantly increased macrolide resistance in oropharyngeal *streptococci*. The bacterial resistance caused by macrolide therapy mandates a cautious application of this therapy in clinical practice. Further studies are needed to evaluate the possibility that *P aeruginosa*–infected individuals with frequent exacerbations may represent an appropriate subgroup for limitation of this therapy.

Author Contributions: Dr Serisier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: McGuckin, Bowler, Serisier.

Acquisition of data: Martin, Lourie, Chen, Brain, Biga, Schlebusch, Dash, Bowler, Serisier.

Analysis and interpretation of data: McGuckin, Schlebusch, Serisier.

Drafter of the manuscript: Serisier.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: McGuckin, Serisier.

Administrative, technical, or material support: Martin, McGuckin, Lourie, Brain, Biga, Schlebusch, Dash, Bowler, Serisier.

Study supervision: McGuckin, Lourie, Schlebusch, Serisier.

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