

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

## The BLESS Randomized Controlled Trial

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**T**HE PATHOPHYSIOLOGY OF NON-cystic fibrosis (CF) bronchiectasis is generally considered to be characterized by an airway inflammatory response to bacterial pathogens, and recent data provide further evidence to support this “vicious cycle” hypothesis.<sup>1</sup> However, studies of maintenance therapies designed to interrupt this cycle at differing points have failed to demonstrate convincing evidence of clinical efficacy, including prolonged oral antibiotics,<sup>2</sup> inhaled tobramycin,<sup>3</sup> inhaled corticosteroids,<sup>4</sup> and mucolytics.<sup>5</sup> Until recently,<sup>6</sup> there have arguably been no therapies with proven clinical benefit in non-CF bronchiectasis.

Maintenance azithromycin was shown to reduce exacerbations in non-CF bronchiectasis<sup>6</sup>; however, limitations of that study<sup>7</sup> included a treatment period of only 6 months and a lack of systematic evaluation for macrolide

**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 *Pseudomonas aeruginosa* airway infection (mean difference, 1.32 [95% CI, 0.19-2.46];  $P = .02$ ). Erythromycin reduced 24-hour sputum production (median difference, 4.3 g [interquartile range [IQR], 1 to 7.8],  $P = .01$ ) and attenuated lung function decline (mean absolute difference for change in postbronchodilator forced expiratory volume in the first second of expiration, 2.2 percent predicted [95% CI, 0.1% to 4.3%];  $P = .04$ ) compared with placebo. Erythromycin increased the proportion of macrolide-resistant oropharyngeal streptococci (median change, 27.7% [IQR, 0.04% to 41.1%] vs 0.04% [IQR, -1.6% to 1.5%]; difference, 25.5% [IQR, 15.0% to 33.7%];  $P < .001$ ).

**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.

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resistance development. Erythromycin offers macrolide-related clinical benefits<sup>8</sup> with a lower risk of induction of macrolide resistance than azithromycin.<sup>9-13</sup> It is also substantially cheaper than azithromycin (in Australia, annual cost approximately US \$190 for 400 mg twice daily<sup>14</sup> vs US \$1200 for azithromycin, 500 mg, 3 times weekly<sup>15</sup>) 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<sub>1</sub>] 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 cul-

tures 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.

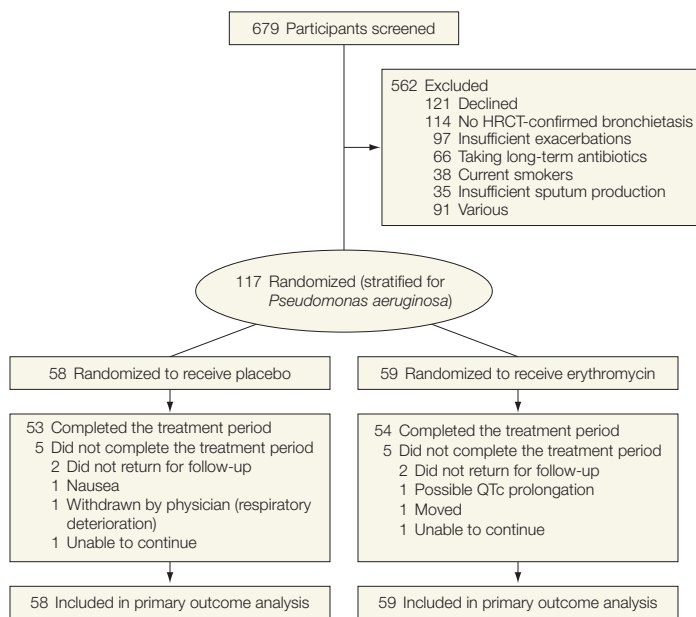
Participants visited the center for examinations 3 times in the first 8 weeks and a total of 8 times over 40 weeks (during this period, they were also contacted by telephone every 4 weeks, between visits); each participant had a final follow-up visit at week 52 after the 4-week washout period (eFigure 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 com-

pleted 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).<sup>9</sup> (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 antibiotic tolerance. Deteriorations in respiratory symptoms that did not meet criteria for PDPEs were termed *non-protocol-defined PE*s (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-

**Figure 1.** Flow of Patients Through the Trial

Participants who were clearly ineligible on the basis of initial telephone screening for key inclusion criteria did not proceed to a full screening visit ( $n=429$ ). The most common reasons for exclusion were as follows: bronchiectasis diagnosis not confirmed (105), insufficient exacerbations (79), declined (74), current smokers (37), insufficient sputum production (33). HRCT indicates high-resolution computed tomography; QTc, corrected QT interval.

tum volume or purulence accompanied by new deteriorations in at least 2 additional symptoms: sputum volume, sputum purulence, cough, dyspnea, chest pain, or hemoptysis.

Secondary end points included the rate of all pulmonary events (ie, PDPEs plus non-PDPEs) for which participants commenced antibiotics, total days of antibiotics, change in the proportion of commensal oropharyngeal streptococci resistant to macrolides, symptoms (Leicester cough questionnaire), quality of life (SGRQ), 24-hour sputum weight, FEV<sub>1</sub> percent predicted, C-reactive protein level, exercise capacity (6-minute walk test result), sputum bacteriology, and sputum inflammatory cell counts. Safety end points included adverse events, liver function test results, and electrocardiograms. Adherence was assessed at each visit by pill counts. A single prespecified subgroup analysis was performed, of PDPEs according to the presence of sputum *P aeruginosa* at baseline.

### Data Analysis

Assuming a baseline (SD) annual rate of exacerbations in the control group of 2.9 (1.2),<sup>16</sup> 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 uncontrolled pilot data.<sup>17</sup> Assuming 20% attrition, the required sample size was increased to 118.

A Poisson regression model was used to analyze the primary outcome measure, evaluating both events and exposure (person-time), employing a quasi-likelihood factor (with overdispersion correction), and incorporating the following covariables: treatment assignment, age, sex, smoking history, and presence of *P aeruginosa* at baseline. Secondary outcomes (including the subgroup analysis) were assessed using different measures according to the outcome and data distribution but included analysis of covariance (using base-

line values as the covariate and provided assumptions of normality and linearity were met), nonparametric tests, and Fisher exact test. Assessment of interaction was performed by testing the heterogeneity of treatment effects between subgroups using the method described by Matthews and Altman.<sup>18</sup> All noncumulative end points were analyzed as the change between weeks 0 and 48, comparing difference in change between placebo and erythromycin with last-observation-carried-forward (LOCF) analyses for missing data and, as a sensitivity analysis, multiple imputation of missing data. All reported results are for the intention-to-treat population. Measures of effect are reported with 95% confidence intervals unless otherwise indicated. All analyses were 2-sided, and *P* values <.05 were considered significant. Statistical analyses were performed using StatsDirect statistical software (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 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

114 for placebo; mean, 1.29 [95% CI, 0.93-1.65] vs 1.97 [95% CI, 1.45-2.48], respectively, per patient per year; incidence rate ratio [IRR], 0.57 [95% CI, 0.42-0.77];  $P=.003$  (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). Intravenous antibiotics were administered for PDPEs on 16 occasions (6 episodes in 5 erythromycin participants, 10 episodes in 7 placebo participants).

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 FEV<sub>1</sub> percent predicted across the study (TABLE 2). Post hoc analysis using the mean of all FEV<sub>1</sub> percent-predicted

measurements during the treatment period to reduce variability<sup>5</sup> 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 1.** Baseline Demographics and Disease Characteristics<sup>a</sup>

	Placebo (n = 58)	Erythromycin (n = 59)
Age, mean (SD), y	63.5 (9.5)	61.1 (10.5)
Female sex, No. (%)	33 (56.9)	38 (64.4)
FEV <sub>1</sub> , mean (SD)		
Prebronchodilator, L	1.83 (0.77)	1.82 (0.65)
Prebronchodilator, % predicted	70.1 (20.3)	66.9 (17.2)
Postbronchodilator, L	1.93 (0.79)	1.93 (0.65)
Postbronchodilator, % predicted	73.6 (20.6)	70.2 (17.2)
<i>Pseudomonas aeruginosa</i> , No. (%) <sup>b</sup>		
At screening visit	17 (29.3)	17 (28.8)
At baseline (screening or visit 1)	18 (31.0)	23 (39.0)
Other sputum pathogens at screen, No. (%)		
<i>Haemophilus influenzae</i>	12 (20.7)	12 (20.3)
"Normal flora" (no pathogens)	27 (46.6)	26 (44.1)
≥5 Exacerbations in prior year, No. (%)	20 (34.5)	22 (37.3)
Exsmokers, No. (%)	15 (25.9)	10 (16.9)
Smoking history, mean (SD), pack-years	2.9 (7.1)	2.3 (10.7)
Median (IQR)	0 (0-2)	0 (0-0)
24-hour sputum weight, median (IQR), g	18.4 (11.8-27.1)	15.4 (9.1-23.7)
SGRQ total score, mean (SD) <sup>c</sup>	38.1 (15.4)	36.7 (13.7)
LCQ score, mean (SD) <sup>d</sup>	14.7 (3.4)	15.1 (3.0)
6-min walk test, median (IQR), m	515 (450-582)	510 (480-555)
C-reactive protein, median (IQR), mg/L	3.55 (0.8-7)	3.20 (1.3-8.5)
Sputum neutrophils, median (IQR), % <sup>e</sup>	96.0 (90.7-97.1)	96.9 (95.1-97.7)
Sputum eosinophils, median (IQR), % <sup>e</sup>	0.5 (0.2-1.0)	0.5 (0.2-0.8)
Medications, No.		
Combination inhalers, ICS/LABA	23	28
Inhaled SABA	18	31
Inhaled anticholinergics	10	8
Inhaled corticosteroids alone	8	5
Inhaled LABA alone	0	4
Prednisolone	3	0
Nebulized saline	1	1
Bromhexine	1	3
Inhaled mannitol	0	1
Nebulized colistin	0	1
Comorbidities, No.		
Hypertension	20	17
Asthma	10	12
Ischemic heart disease	6	5
Cerebrovascular disease	4	2
Diabetes mellitus	2	1

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in the first second; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, long-acting β-agonists; LCQ, Leicester cough questionnaire; SABA, short-acting β-agonists; SGRQ, St George's Respiratory Questionnaire.

<sup>a</sup>There were no significant between-group differences.

<sup>b</sup>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.

<sup>c</sup>Lower scores indicate better quality of life.

<sup>d</sup>Lower scores indicate worse cough symptoms (range, 3-21).

<sup>e</sup>Percentage of total nonsquamous cells.



eTable 2). 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 medi-

cation. 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 demon-

strate any significant between-group differences for any measure (eResults).

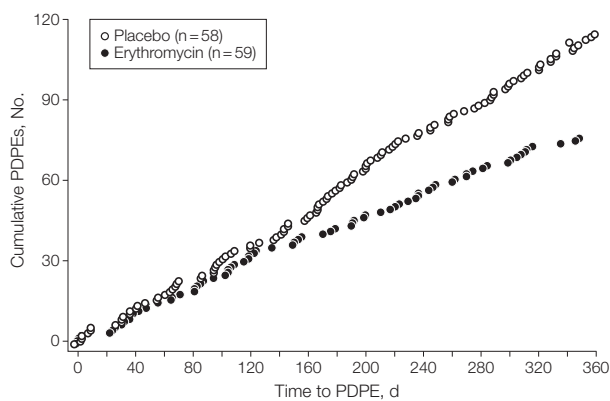
**Adverse Events and Additional Analyses**

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 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).

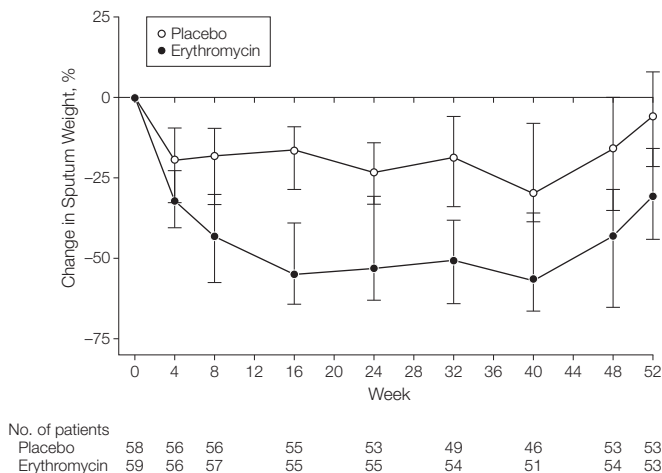
Exploratory subgroup analyses according to degree of sputum neutrophilia and *Haemophilus influenzae* infection showed no evidence of subgroup benefit. The subgroup with very high baseline pulmonary exacerbation rate ( $\geq 5$  exacerbations in the preceding year) did show a benefit with erythromycin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

**Figure 2.** Cumulative Occurrence of Protocol-Defined Pulmonary Exacerbations



Each point represents a separate protocol-defined pulmonary exacerbation (PDPE). Individual participants could account for more than 1 event each.  $P = .003$  for the comparison with placebo for the rate of pulmonary exacerbations per patient per year.

**Figure 3.** Median Change in 24-Hour Sputum Weight From Baseline



The baseline value is expressed as 0, with subsequent values representing proportional change from baseline, expressed as a percentage, such that any value at point  $x = 100 \times (\text{value } x - \text{baseline value}) / \text{baseline value}$ .  $P = .01$  for the comparison of placebo and erythromycin for change between visit 1 (week 0) and visit 8 (week 48). Error bars represent 95% CI.

**COMMENT**

In patients with non-CF bronchiectasis with a history of frequent pulmonary ex-

acerbations, low-dose erythromycin reduced pulmonary exacerbations, decreased sputum production, attenuated lung function decline, and appeared to increase rates of eradication of sputum pathogens. BLESS represents the longest published study of macrolide therapy in non-CF bronchiectasis to date, the only long-term randomized controlled trial of erythromycin, and the most comprehensive assessment to date of the ecological consequences of long-term macrolide therapy.

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 erythromycin<sup>19</sup> and greater than reported with azithromycin (0.35)<sup>20</sup> in chronic obstructive pulmonary disease, although somewhat less than the 0.98 reduction recently reported with azithromycin in bronchiectasis.<sup>6</sup> The definition of exacerbation in that study differed from the current study (BLESS required deteriorations in 3 symptoms rather than 2), 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 in-

tolerance. 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,<sup>21</sup> strongly related to concomitant use of strong inhibitors of cytochrome P-450 3A (CYP3A) enzymes.<sup>22</sup> 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.<sup>23</sup>

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 patient population and relative underpowering for this end point. The EMBRACE trial also failed to demonstrate significant improvement in SGRQ.<sup>6</sup>

**Table 2.** Secondary Outcome Measures<sup>a</sup>

	Change From Baseline to Visit 8		Treatment Effect (95% CI) <sup>b</sup>
	Placebo (n = 58)	Erythromycin (n = 59)	
Postbronchodilator FEV <sub>1</sub> , mean (SD), % predicted	-4.0 (6.6)	-1.6 (4.6)	2.2 (0.1 to 4.3) <sup>c</sup>
Median (IQR)	-3.36 (-7.86 to 0)	-1.41 (-5.03 to 1.06)	
24-hour sputum weight, median (IQR), g	-1.7 (-8.2 to 2.6)	-5.4 (-16.0 to -1.3)	-4.3 (-7.8 to -1) <sup>d</sup>
SGRQ total score, mean (SD) <sup>e</sup>	-1.3 (14.5)	-3.9 (10.0)	-2.9 (-7.3 to 1.6)
Median (IQR)	-2.8 (-8.8 to 8.4)	-3.7 (-8.5 to 4.2)	
SGRQ symptom score, mean (SD)	-3 (24.3)	-6 (23.5)	-5.3 (-12.6 to 2.1)
Median (IQR)	0.3 (-18.7 to 12.4)	-8.5 (-18.4 to 15.7)	
LCQ score, mean (SD) <sup>f</sup>	0.52 (3.0)	1.16 (3.1)	0.79 (-0.2 to 1.8)
6-min walk test, median (IQR), m	0 (-23 to 25)	2 (-12 to 18)	3.55 (-17.6 to 24.7)
CRP, median (IQR), mg/L <sup>g</sup>	-0.5 (-2.1 to 1.0)	-0.7 (-2.7 to 1.6)	-0.2 (-1.5 to 1.2)
Sputum neutrophils, median (IQR), % <sup>h</sup>	0.75 (-1.2 to 3.5)	-0.8 (-4.8 to 1.0)	-2.1 (-5 to 0)

Abbreviations: CRP, C-reactive protein; FEV<sub>1</sub>, forced expiratory volume in the first second; IQR, interquartile range; LCQ, Leicester cough questionnaire; SGRQ, St George's Respiratory Questionnaire.

<sup>a</sup>All results are for the intention-to-treat population.

<sup>b</sup>Treatment 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.

<sup>c</sup>*P* = .04.

<sup>d</sup>*P* = .01.

<sup>e</sup>Lower scores indicate better quality of life.

<sup>f</sup>Lower scores indicate worse cough symptoms (range, 3-21).

<sup>g</sup>Missing baseline values for CRP limited the analysis to 54 erythromycin and 50 placebo participants. Missing data were not imputed for this outcome.

<sup>h</sup>Neutrophils 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.

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 or 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,<sup>24</sup> accelerated lung function decline,<sup>25</sup> and increased mortality.<sup>26</sup> 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.<sup>27</sup> The magnitude of the placebo group FEV<sub>1</sub> decline was identical to that seen in the largest published study in non-CF bronchiectasis to date<sup>5</sup> (using equivalent methodology, 3.4% over 48 weeks in BLESS vs 1.7% over 24 weeks).<sup>5</sup> Erythromycin provided significant protection against this decline across the study, an effect not seen in the recently published azithromycin study.<sup>6</sup> 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 finding as it suggests the potential for erythromycin to influence the natural history of this condition, in addition to 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.<sup>19,20</sup> A study of azithromycin given to volunteers for 3 days<sup>9</sup> 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,<sup>11-13,27</sup> an effect implied by its long half-life, which allows for extended periods of subinhibitory concentrations.<sup>28</sup> 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,<sup>29</sup> including the demonstration of alterations to *P aeruginosa* morphology and inhibition of adherence to respiratory epithelium with erythromycin exposure in vitro.<sup>30</sup> Additionally, erythromycin significantly reduced sputum production. This may represent direct attenuation of mucus secretion, as has been demonstrated in murine and in vitro studies,<sup>31</sup> although reduced mucus production is probably also a predictable consequence of antibacterial or anti-inflammatory effects.<sup>32</sup>

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.

**Drafting 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.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Serisier reported receiving honoraria for serving on the medical advisory boards of Pharmaxis, Phebra, Boehringer-Ingelheim, and GlaxoSmithKline; speaker's fees for presenting at educational meetings organized by GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, and Pharmaxis; and travel support from Boehringer-Ingelheim to attend a scientific meeting. Dr Bowler reported receiving honoraria for serving on the medical advisory board of Novartis; speaker's fees for presenting at educational meetings organized by AstraZeneca, GlaxoSmithKline, and Boehringer-Ingelheim; and travel support from GlaxoSmithKline to attend scientific meetings. No other disclosures were reported.

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