Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial

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Summary

Background **Azithromycin is a macrolide antibiotic with anti-inflammatory and immunomodulatory properties. We tested the hypothesis that azithromycin would decrease the frequency of exacerbations, increase lung function, and improve health-related quality of life in patients with non-cystic fibrosis bronchiectasis.**

Methods **We undertook a randomised, double-blind, placebo-controlled trial at three centres in New Zealand. Between Feb 12, 2008, and Oct 15, 2009, we enrolled patients who were 18 years or older, had had at least one pulmonary exacerbation requiring antibiotic treatment in the past year, and had a diagnosis of bronchiectasis defined by high-resolution CT scan. We randomly assigned patients to receive 500 mg azithromycin or placebo three times a week for 6 months in a 1:1 ratio, with a permuted block size of six and sequential assignment stratified by centre. Participants, research assistants, and investigators were masked to treatment allocation. The coprimary endpoints were rate of event-based exacerbations in the 6-month treatment period, change in forced expiratory volume in 1 s (FEV_1) before bronchodilation, and change in total score on St George's respiratory questionnaire (SGRQ). Analyses were by intention to treat. This study is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12607000641493.**

Findings **71 patients were in the azithromycin group and 70 in the placebo group. The rate of event-based exacerbations was 0·59 per patient in the azithromycin group and 1·57 per patient in the placebo group in the 6-month treatment period (rate ratio 0·38, 95% CI 0·26–0·54; p<0·0001). Prebronchodilator FEV_1 did not change from baseline in the azithromycin group and decreased by 0·04 L in the placebo group, but the difference was not significant (0·04 L, 95% CI –0·03 to 0·12; p=0·251). Additionally, change in SGRQ total score did not differ between the azithromycin (–5·17 units) and placebo groups (–1·92 units; difference –3·25, 95% CI –7·21 to 0·72; p=0·108).**

Interpretation **Azithromycin is a new option for prevention of exacerbations in patients with non-cystic fibrosis bronchiectasis with a history of at least one exacerbation in the past year.**

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Introduction

Bronchiectasis is a disorder characterised by neutrophilic airway inflammation, chronic bacterial infection, and recurrent pulmonary exacerbations.[1] Patients with bronchiectasis can have a disabling cough with production of large amounts of sputum, progressive decline in lung function,[2] impaired quality of life,[3,4] and increased mortality.[5,6] Exacerbations occur at rates of 1·5–6·5 per patient per year,[7,8] and are associated with an increased risk of admission and readmission to hospital, and high healthcare costs.[9]

The prevalence of bronchiectasis in most adult populations worldwide is unknown. With the widespread availability of modern diagnostic techniques such as high-resolution CT scanning, bronchiectasis is increasingly being recognised. In the USA, the number of bronchiectasis-associated admissions increased by 2–3% per year between 1993 and 2006, and the mean annual rate of admission in this period was 16·5 per 100 000 people.[9] A further study[10] showed that the prevalence of bronchiectasis increased by 8·7% per year between 2000 and 2007.

Few evidence-based treatments are available for the prevention and management of exacerbations and more are urgently needed.[11] Macrolide antibiotics have anti-inflammatory and immunomodulatory properties in addition to their antibacterial properties.[12] In the Effectiveness of Macrolides in patients with BRonchiectasis using Azithromycin to Control Exacerbations (EMBRACE) trial, we tested whether azithromycin decreases the frequency of exacerbations, increases lung function, and improves health-related quality of life in patients with non-cystic fibrosis bronchiectasis.

Methods

Study design and participants

We undertook a randomised, double-blind, placebo-controlled trial at three centres in New Zealand between Feb 12, 2008, and Oct 15, 2009. Patients were eligible for inclusion in the study when they were 18 years or older, had had at least one pulmonary exacerbation requiring antibiotic treatment in the past year, and had a diagnosis of bronchiectasis defined by high-resolution CT scan. All

CT scans were reviewed centrally by one respiratory radiologist (DM) to verify the diagnosis of bronchiectasis before randomisation.[13]

Exclusion criteria were history of cystic fibrosis; hypogammaglobulinaemia; allergic bronchopulmonary aspergillosis; a positive culture of non-tuberculous mycobacteria in the past 2 years or at screening; macrolide treatment for more than 3 months in the past 6 months; or unstable arrhythmia.

Participants provided written informed consent. The study was approved by an independent regional ethics committee. An independent data and safety monitoring committee of the Health Research Council (HRC) of New Zealand oversaw the study.

Randomisation and masking

Eligible patients were randomly assigned to receive either azithromycin or placebo by a statistician independent to the reporting statistician with a computer-generated random number list. Patients were randomly assigned in a 1:1 ratio, with a permuted block size of six and sequential assignment, stratified by centre. Participants, research assistants, and investigators were masked to treatment allocation.

Procedures

Patients were given either 500 mg azithromycin or matching placebo to take on 3 days (Monday, Wednesday, and Friday) every week for 6 months. They were then followed up for another 6 months without treatment. Clinic visits were scheduled at weeks 4, 13, 26, 39, and 52, and monthly telephone calls were scheduled between visits. Patients completed a daily symptom diary card. Adherence was assessed by pill counts. Data were gathered for spirometry, St George's respiratory questionnaire (SGRQ),[4] the 6-min walk test (6MWT),[14] concentration of C-reactive protein, and adverse events.

We obtained spontaneous sputum samples for cell counts and culture of respiratory pathogens. Every unselected sample was dispersed with dithiothreitol and filtered, and we assessed total cell count and viability. We centrifuged the cell suspension and prepared cytospins. We obtained a differential cell count from 400 non-squamous cells.[15]

We had three coprimary endpoints: rate of event-based exacerbations in the first 6 months, forced expiratory volume in 1 s (FEV_1) before bronchodilation, and SGRQ total score at the end of the treatment period. An event-based exacerbation was defined as an increase in or new onset of more than one pulmonary symptom (sputum volume, sputum purulence, or dyspnoea) requiring treatment with antibiotics. The patient's general practitioner or physician, who was masked to treatment allocation, decided whether to treat exacerbations with antibiotics. At enrolment, we corresponded with the patients' general practitioners, recommending avoidance of macrolide antibiotics for treatment of pulmonary exacerbations.

Secondary endpoints were time to first exacerbation, rate of symptom-based exacerbations, prebronchodilator and postbronchodilator forced vital capacity (FVC), postbronchodilator FEV_1, exercise capacity (as measured by the 6MWT), SGRQ total score at 12 months, concentration of C-reactive protein (assessed only at 6 months), sputum cell counts and microbiology, and adverse events. For a symptom-based exacerbation to be recorded, the patient had to have an increase in or new onset of more than one pulmonary symptom reported on the daily diary card and the mean of the three symptom scores from the daily diary card on 2 consecutive days had to increase by at least one point (on a five-point scale) compared with the same calculation 1 week earlier. All exacerbations were adjudicated by a committee, who confirmed that the exacerbations met the study definition of an event-based or symptom-based exacerbation and that events were new and independent of any previous events.

Statistical analysis

We estimated that about 134 patients would need to be enrolled for the study to have 80% power to detect a 33% difference in the Poisson frequency of exacerbations in the 6-month treatment period between the two groups, assuming a two-sided α level of 0·05 and a 10% dropout rate. With the assumption of normality, the study had a power of 89% to detect a difference of 0·16 L in the prebronchodilator FEV_1 and a power of 87% to detect a difference of eight units in SGRQ total score. All analyses were done by intention to treat.

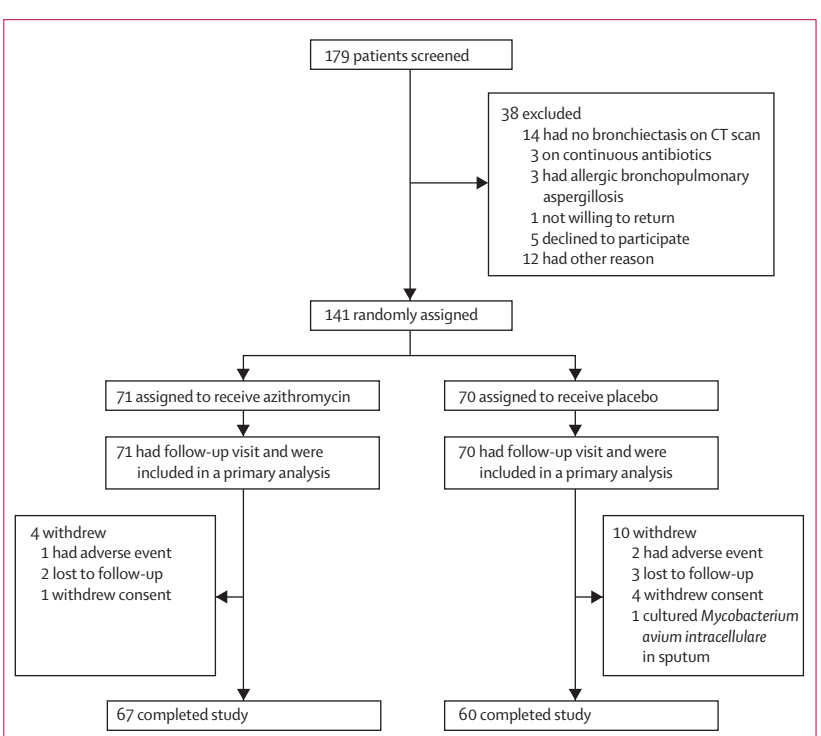

Figure 1: **Trial profile**

	Azithromycin group (n=71)	Placebo group (n=70)
Men	23 (32%)	20 (29%)
Age (years)	60·9 (13·6)	59·0 (13·3)
Smoking status		
Present smokers	1 (1%)	4 (6%)
Smoking history (pack-years)	5·1 (10·2)	8·8 (17·4)
Asthma	13 (18%)	14 (20%)
Body-mass index (kg/m^2)	28·8 (7·2)	28·6 (6·9)
Ethnic origin		
European	43 (61%)	52 (74%)
Polynesian	13 (18%)	12 (17%)
Maori	11 (16%)	5 (7%)
Other	4 (6%)	1 (1%)
Exacerbations in past year	3·34 (2·16)	3·93 (2·49)
Spirometry before bronchodilation		
FEV_1 (L)	1·87 (0·74)	1·88 (0·69)
Percentage of predicted FEV_1	67·1% (21·2)	67·3% (23·2)
FVC (L)	2·82 (0·85)	2·87 (0·79)
Percentage of predicted FVC	77·7% (17·5)	78·5% (18·1)
FEV_1/FVC	65·4% (12·5)	64·7% (11·8)
Spirometry after bronchodilation		
FEV_1 (L)	1·94 (0·74)	1·95 (0·71)
Percentage of predicted FEV_1	69·4% (20·8)	69·3% (23·4)
FVC (L)	2·89 (0·85)	2·96 (0·82)
Percentage of predicted FVC	79·3% (17·2)	80·1% (18·2)
FEV_1/FVC	66·4% (12·9)	65·2% (12·2)
Total score on St George's respiratory questionnaire*	31·9 (17·8)	36·6 (19·4)
Symptoms	47·9 (2·5)	51·7 (2·7)
Activity	40·8 (2·6)	46·7 (2·9)
Impacts	24·2 (2·1)	29·5 (2·3)
(Continues in next column)		

	Azithromycin group (n=71)	Placebo group (n=70)
(Continued from previous column)		
6-minute walk test distance (m)	510·8 (102·6)	509·6 (105·3)
C-reactive protein (mg/L)†	2·91	3·25
Peripheral blood cells†		
White blood cells (×10^9/mL)	6·69	7·67
Neutrophils (×10^9/mL)	4·01	4·49
Eosinophils (×10^9/mL)	0·24	0·23
Sputum cell counts†		
Total cells (×10^9/mL)	3·21	4·55
Neutrophils (%)	68·44%	68·51%
Eosinophils (%)	2·15%	1·71%
Bronchial epithelial cells (%)	6·00%	5·95%
Respiratory drugs		
Any	59 (83%)	60 (86%)
Inhaled anticholinergic		
Shortacting	8 (11%)	5 (7%)
Longacting	1 (1%)	6 (9%)
β_2 agonists		
Shortacting	24 (34%)	33 (47%)
Longacting	6 (9%)	10 (14%)
Corticosteroid		
Inhaled	18 (25%)	23 (33%)
With longacting β_2 agonists	11 (16%)	16 (23%)
Oral	2 (3%)	0
Mucolytic agent	1 (1%)	2 (3%)
Leukotriene-receptor antagonist	0	0

Data are n (%) or mean (SD), unless otherwise stated. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Scores range from 0 to 100, with low scores indicating improvement; a change of four or more units is deemed clinically meaningful. †Geometric means.

Table 1: **Baseline characteristics of patients**

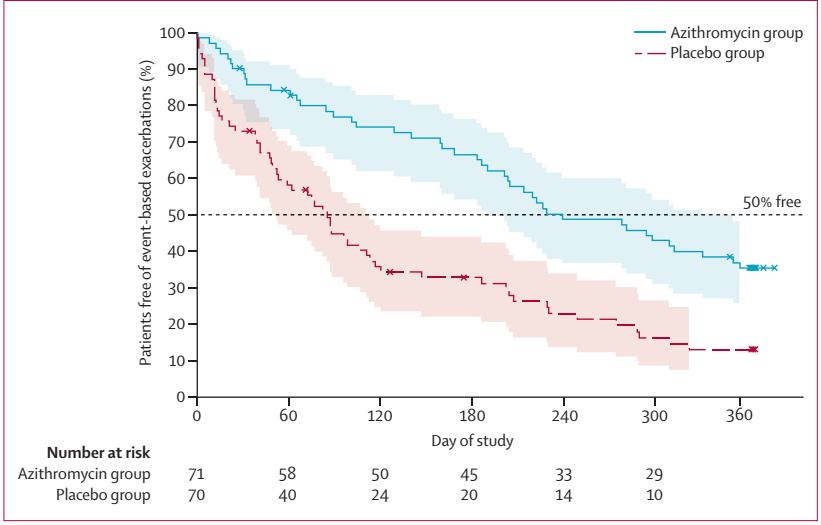

Figure 2: **Proportion of participants free from event-based exacerbations**
Shaded areas indicate 95% CIs. Crosses indicate censoring.

Numbers of exacerbations were compared between groups with a Poisson regression model that allowed for the individual lengths of study period. Time to first exacerbation was analysed with a Cox proportional hazard regression model and presented with Kaplan-Meier plots. Descriptive statistics were counts and percentages for categorical variables, means and SDs for normally distributed variables, and geometric means for skewed variables that were log transformed to give a normal distribution. We analysed variables for which we had baseline data as change from baseline and included the baseline value of the response as a covariate, centre as the stratifying factor, and demographic variables age, race, and sex. Interactions between treatment and prognostic variables were examined to explore the possibility that response to treatment varied in size dependent on the value of the prognostic variable. We did all analyses in SAS (version 9.2).

This study is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12607000641493.

Role of the funding source
The sponsor had no role in study design, data collection, data analysis, or data interpretation. The data monitoring committee of the sponsor provided feedback on the completed report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
141 patients underwent randomisation and all patients received at least one dose of the assigned treatment (figure 1). Table 1 shows baseline characteristics and concomitant use of respiratory medications. Fewer patients in the azithromycin group than in the placebo group withdrew from the study prematurely (figure 1). We established from pill counts that patients adhered 97·9% of the time in the azithromycin group and 98·3% of the time in the placebo group.

42 event-based exacerbations were recorded in the azithromycin group compared with 103 in the placebo group. The rate of exacerbations was 0·59 per patient in the 6-month treatment period in the azithromycin group and 1·57 per patient in the placebo group, corresponding to a 62% relative reduction with azithromycin (rate ratio 0·38, 95% CI 0·26–0·54; p<0·0001). In the 12-month period, 109 exacerbations were recorded in the azithromycin group compared with 178 in the placebo group. The annual rate of exacerbations was 1·58 per patient in the azithromycin group and 2·73 per patient in the placebo group, corresponding to a 42% relative reduction with azithromycin (0·58, 0·46–0·74; p<0·0001). No exacerbations were treated with azithromycin, which is not funded for treatment of bronchiectasis in New Zealand.

22 (31%) patients in the azithromycin group had at least one event-based exacerbation in the 6-month period, compared with 46 (66%) in the placebo group. Azithromycin reduced the risk of exacerbations by 52% (relative risk 0·48, 95% CI 0·32–0·71; p<0·0001). In 12 months, 44 (62%) patients in the azithromycin group had at least one exacerbation, compared with 58 (83%) in the placebo group, corresponding to a 25% reduction in risk (0·75, 0·61–0·93; p=0·005).

Because less than 50% of patients in the azithromycin group had an event-based exacerbation at 6 months, the median time to first exacerbation could not be compared for this period; the time until at least 25% of the patients had a first exacerbation was used instead. This time was much higher in the azithromycin group than in the placebo group (104 [95% CI 48–186] *vs* 21 days [11–48]; hazard ratio 0·34, 95% CI 0·20–0·56; p<0·0001). In the 12-month period, median time to first exacerbation was greater in the azithromycin group than in the placebo group (239 [190–331] *vs* 85 days [52–113]; 0·44, 0·29–0·65; p<0·0001; figure 2).

Groups did not differ significantly in annual rate of symptom-based exacerbations (data not shown). Additionally, groups did not differ in time to the first symptom-based exacerbation for the 6-month and 12-month study periods (data not shown).

Changes in prebronchodilator and postbronchodilator FEV_1 from baseline to 6 and 12 months did not differ significantly between groups (table 2). Changes in prebronchodilator and postbronchodilator FVC to 6 and 12 months were higher in the azithromycin group than in the placebo group (table 2). The changes in FEV_1 and FVC were in the same direction and were strongest for the postbronchodilator values (table 2).

	Change from baseline		Difference (95% CI)	p value
	Azithromycin group	Placebo group		
After 6 months of treatment				
Prebronchodilator FEV_1 (L)	0	−0·04	0·04 (−0·03 to 0·12)	0·251
Postbronchodilator FEV_1 (L)	−0·01	−0·08	0·07 (−0·03 to 0·15)	0·055
Prebronchodilator FVC (L)	−0·02	−0·10	0·08 (−0·03 to 0·18)	0·069
Postbronchodilator FVC (L)	−0·01	−0·14	0·13 (−0·04 to 0·23)	0·007
Score on St George's respiratory questionnaire*				
Total	−5·17	−1·92	−3·25 (−7·21 to 0·72)	0·108
Symptoms	−10·69	−3·99	−6·70 (−13·37 to −0·04)	0·049
Activity	−0·93	0·64	−1·58 (−7·31 to 4·12)	0·587
Impacts	−4·60	−0·86	−3·73 (−8·23 to 0·75)	0·102
6-min walk test distance (m)	0·88	−9·63	10·52 (−5·12 to 26·15)	0·185
Concentration of C-reactive protein	−13·8%	40·1%	−38·4 (−56·4 to −13·2)	0·006
Peripheral blood cells				
White blood cells	−8·9%	3·6%	−12·0 (−20·5 to −2·7)	0·013
Neutrophils	−16·1%	−1·8%	−14·6 (−25·4 to −2·3)	0·022
Eosinophils	−8·0%	8·1%	−14·9 (−26·9 to −0·9)	0·038
Sputum cell counts				
Total	31·8%	100·2%	−34·2 (−66·8 to 30·3)	0·227
Neutrophils	−7·9%	9·3%	−15·7 (−30·6 to 2·5)	0·129
Eosinophils	−13·7%	−3·6%	−10·4 (−35·1 to 23·6)	0·951
Bronchial epithelial cells	66·4%	−13·7%	92·7 (8·8 to 240·8)	0·025
After 12 months				
Prebronchodilator FEV_1 (L)	−0·02	−0·06	0·04 (−0·02 to 0·11)	0·175
Postbronchodilator FEV_1 (L)	−0·01	−0·06	0·07 (−0·01 to 0·15)	0·092
Prebronchodilator FVC (L)	−0·04	−0·13	0·09 (0 to 0·18)	0·049
Postbronchodilator FVC (L)	−0·04	−0·15	0·11 (0·01 to 0·21)	0·026
Score on St George's respiratory questionnaire*				
Total	−2·89	−4·71	1·82 (−0·27 to 6·32)	0·425
Symptoms	−9·72	−8·22	−1·51 (−9·05 to 6·04)	0·693
Activity	1·16	−1·55	2·71 (−3·37 to 8·79)	0·378
Impacts	−1·03	−5·32	4·29 (−0·90 to 9·47)	0·104
6-min walk test distance (m)	1·19	−5·28	6·48 (−11·28 to 24·22)	0·471
Sputum cell counts				
Total	−22·0	23·0	−36·6 (−68·7 to 28·5)	0·203
Neutrophils	7·8	53·1	−29·6 (−50·6 to 0·3)	0·052
Eosinophils	13·5	13·8	−0·2 (−38·1 to 61·0)	0·994
Bronchial epithelial cells	68·0	−25·7	126·1 (25·6 to 307·1)	0·007

FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Scores range from 0 to 100, with low scores indicating improvement; a change of four or more units is deemed clinically meaningful.

Table 2: **Outcome variables**

	At baseline		Eradicated at 6 months		Newly detected at 6 months	
	Azithromycin group (n=71)	Placebo group (n=70)	Azithromycin group (n=46)	Placebo group (n=45)	Azithromycin group (n=46)	Placebo group (n=45)
Haemophilus influenzae	19 (27%)	21 (30%)	14 (30%)	8 (18%)	2 (4%)	6 (13%)
Pseudomonas aeruginosa	9 (13%)	8 (11%)	5 (11%)	5 (11%)	2 (4%)	0
Moraxella catarrhalis	3 (4%)	2 (3%)	3 (7%)	1 (2%)	0	3 (7%)
Staphylococcus aureus	2 (3%)	2 (3%)	2 (4%)	2 (4%)	0	1 (2%)
Streptococcus pneumoniae	1 (1%)	3 (4%)	1 (2%)	2 (4%)	2 (4%)*	0

Data are n (%). Sputum microbiology was documented for the common respiratory pathogens. *Both organisms were resistant to macrolides.

Table 3: **Sputum microbiology at baseline and after 6 months of treatment**

	Azithromycin group (n=71)	Placebo group (n=70)	Total (n=141)
Any adverse events	59 (83%)	65 (93%)	124 (88%)
Severe adverse events	4 (6%)	9 (13%)	13 (9%)
Most frequent adverse events*			
Gastrointestinal	19 (27%)	9 (13%)	28 (20%)
Diarrhoea	13 (18%)	4 (6%)	17 (12%)
Nausea or vomiting	9 (13%)	5 (7%)	14 (10%)
Epigastric discomfort	5 (7%)	1 (1%)	6 (4%)
Constipation	2 (3%)	0	2 (1%)
Common cold	9 (13%)	12 (17%)	21 (15%)
Headache	3 (4%)	3 (4%)	6 (4%)
Sinusitis	3 (4%)	2 (3%)	5 (4%)
Cough	3 (4%)	2 (3%)	5 (4%)
Chest pain	2 (3%)	2 (3%)	4 (3%)

*Those with an incidence of more than 2·5% in either study group.

Table 4: **Adverse events**

The mean change in SGRQ total score at 6 and 12 months did not differ significantly between groups (table 2). There was a greater decrease (ie, an improvement) in the symptom component of the SGRQ in the azithromycin group than in the placebo group at 6 months, but no significant difference was noted at 12 months (table 2). Mean change in SGRQ component scores of activities and impacts at 6 and 12 months did not differ significantly (table 2). We recorded no significant differences between study groups in the 6MWT from baseline to 6 or 12 months (table 2).

Concentrations of C-reactive protein were measured at baseline and 6 months only (no test at 12 months because no other blood tests were being done at this stage). Concentrations decreased in the azithromycin group, but increased in the placebo group at 6 months (table 2). We did peripheral blood counts to monitor adverse events, but they were not prespecified endpoints. The change in number of peripheral blood neutrophils, white blood cells, and eosinophils from baseline was significantly greater in the azithromycin group than in the control group (table 2). The percentage change in number of neutrophils in sputum of patients did not differ significantly between groups at 6 months or 12 months (table 2). The number of bronchial epithelial cells increased at both 6 months and 12 months in the azithromycin group, but decreased in the placebo group (table 2). No significant treatment effects on total cell counts or number of eosinophils were recorded between baseline and 6 or 12 months (table 2).

At baseline, the microbiology profile for selected respiratory pathogens was similar between the two groups (table 3). Sputum from six (13%) participants in the azithromycin group and ten (22%) in the placebo group cultured new respiratory pathogens after 6 months of treatment (p=0·408). Macrolide resistance testing was not routinely undertaken, but two (4%) patients in the azithromycin group developed macrolide-resistant *Streptococcus pneumoniae* at 6 months (table 3).

Azithromycin's effect on exacerbation rate and time to first exacerbation did not vary with sex, age, smoking status, number of exacerbations or antibiotics in the past year, FEV_1, sputum neutrophil counts, or sputum culture of *Haemophilus influenzae* or *Pseudomonas aeruginosa* (data not shown). However, the treatment difference was significantly greater in patients who had higher SGRQ total scores at baseline than in others (data not shown).

Table 4 shows the number of adverse events reported. During treatment, one patient in the azithromycin group had an exacerbation of bronchiectasis requiring admission, one had an umbilical hernia requiring surgery, one had congestive heart failure, and one had a stroke. In the placebo group, three patients had exacerbations of bronchiectasis requiring admission, and three had non-respiratory infections (infected hip joint replacement and peritonsillar abscess, scrotal abscess, and exacerbation of chronic obstructive pulmonary disease). Additionally, one patient given placebo had carcinoma in situ of the skin of the lower leg, one had infectious gastroenteritis, one had haemoptysis, and one had unstable angina. Of the adverse events reported, gastrointestinal symptoms (nausea, vomiting, diarrhoea, epigastric discomfort, and constipation) were reported more frequently in the azithromycin group than in the placebo group (p=0·005; table 4). Two patients in each group discontinued the study drug because of gastrointestinal symptoms.

Discussion

We have shown that azithromycin treatment for 6 months in patients with non-cystic fibrosis bronchiectasis significantly decreases the rate of event-based exacerbations and increases the time to the first event-based exacerbation compared with placebo. These benefits persisted for 6 months after completion of treatment.

Randomised trials of other macrolides for treatment of non-cystic fibrosis bronchiectasis[16–18] have previously

been undertaken (panel). Five studies in patients with cystic fibrosis[21–25] have investigated the effect of azithromycin on exacerbations as a secondary endpoint. Four[22–25] showed that azithromycin decreased frequency or risk of exacerbations by 35–64%. Although the definition of an exacerbation varied in these studies, our study had similar findings.

Azithromycin did not affect frequency of symptom-based exacerbations in our study. The definition that we used was based on the Anthonisen criteria for exacerbations in patients with chronic obstructive pulmonary disease and bacterial infection, which include shortness of breath, sputum colour, and sputum volume, but not cough.[26] Whether a definition that includes cough—the dominant symptom in patients with bronchiectasis[27]—would have increased the agreement between symptom-based and event-based exacerbations in our trial is unclear. However, exacerbations defined by changes in grouped symptoms are poorly related to event-based exacerbations in chronic obstructive pulmonary disease.[28]

The magnitudes of the positive effects on FEV_1 and FVC were similar to those reported in studies of patients with cystic fibrosis.[29] Three previous studies[16–18] have assessed the effect of macrolide antibiotics on FEV_1 in non-cystic fibrosis bronchiectasis. All were of short duration and only one[17] showed an improvement in FEV_1. The presence of *P aeruginosa* in the airways might change the effect of azithromycin on FEV_1, which is an indirect measure of airway inflammation.[30] A trial of azithromycin in patients with cystic fibrosis who were not infected with *P aeruginosa*[25] showed that the drug had no significant effect on FEV_1 or FVC. By contrast, a meta-analysis of studies in patients with cystic fibrosis who predominantly had chronic infection with *P aeruginosa*[29] established that azithromycin treatment improved FEV_1 by 3·2%. Colonisation by *P aeruginosa* was present at baseline in only 12% of patients in our study.

Azithromycin did not improve health-related quality of life as measured by the SGRQ total score in our study. However, the improvement in the symptom component of the SGRQ in the azithromycin group compared with the placebo group at 6 months was significant and clinically important. In a validation study of the SGRQ in bronchiectasis,[4] symptom score was the component that was most strongly associated with the number of infections (exacerbations) in the previous 12 months.[4]

In our trial, azithromycin had an anti-inflammatory effect both systemically and locally within the airway. Azithromycin has complex immunomodulatory effects on neutrophilic airway inflammation and modulates neutrophil accumulation and activation by inhibition of cytokine production and neutrophil priming, transmigration, and chemotaxis.[31] Neutrophil apoptosis and clearance are also enhanced by azithromycin.[31]

Azithromycin was taken three times a week and was generally well tolerated. Although patients given azithromycin reported gastrointestinal adverse events, most were mild and none were serious. Hearing impairment was not reported by the patients in our study, although we did not undertake audiometry. In a study of patients with chronic obstructive pulmonary disease,[32] audiometry measurements showed that reduction in hearing was 5% greater in the azithromycin group than in the placebo group. However, the investigators noted that the size of the effect was probably overestimated.[32] Azithromycin might have proarrhythmic effects; an investigation[33] showed a small increase in acute cardiovascular mortality with 5 days of azithromycin treatment. This epidemiological study contrasts with both our study and the prospective clinical trials of long-term azithromycin treatment for cystic fibrosis and chronic obstructive pulmonary disease,[29,32] which did not show an increased risk of death or cardiovascular adverse events. Further studies are needed to define the cardiovascular risks of azithromycin.

Our study has some limitations. First, we did not routinely test for macrolide resistance, but other studies[25,32,34] have shown that chronic azithromycin treatment increases the development of macrolide-resistant organisms. Azithromycin could also predispose patients with cystic fibrosis to the development of non-tuberculous

***Panel:* Research in context**

Systematic review

We searched the PubMed and Cochrane databases for full reports of trials published before May 23, 2012, with the terms "bronchiectasis", "azithromycin", "macrolide", "erythromycin", "clarithromycin", "roxithromycin", "exacerbations", and "treatment". We identified three randomised controlled trials[16–18] that assessed macrolide treatment (roxithromycin,[16] erythromycin,[17] and clarithromycin[18]) for non-cystic fibrosis bronchiectasis. These studies were small (<35 patients in each study), were of short duration (≤12 weeks), and did not assess clinically relevant outcomes such as pulmonary exacerbations and quality of life. A Dutch trial[19] showed that patients treated with 250 mg azithromycin daily for 1 year had fewer exacerbations than did the placebo group. Additionally, an Australian trial[20] showed that 400 mg erythromycin twice a day for 48 weeks significantly reduced the frequency of pulmonary exacerbations.

Interpretation

Our results show that azithromycin treatment for 6 months decreases the frequency of exacerbations and increases time to first exacerbation. These benefits persist for 6 months after completion of treatment. Therefore, azithromycin is a new treatment option for patients with non-cystic fibrosis bronchiectasis with a history of at least one exacerbation in the past year. However, we recommend a careful approach to the selection of patients for long-term azithromycin treatment because of increasing concerns about macrolide resistance.

mycobacterial infection.[35] However, colonisation with macrolide-resistant organisms has not been shown to increase exacerbations, and the clinical implications of macrolide-resistant organisms in cystic fibrosis and non-cystic fibrosis bronchiectasis remain unclear.[36]

Second, the frequency of exacerbations in the year before the trial was higher in the placebo group than in the azithromycin group and could have contributed to the difference. We adjusted for this baseline effect in our analysis and a large, significant effect of azithromycin remained. Third, sputum samples were obtained at 6 months from only 65% of the participants in the azithromycin group and 64% in the placebo group. Induced sputum samples would have increased the yield but were not included in our protocol because of resource constraints. Finally, we did not screen for cystic fibrosis, but all patients were adults without a history or clinical characteristics suggestive of cystic fibrosis.

The optimum duration of treatment with azithromycin is unclear but depends on a balance between improvement of important clinical endpoints such as exacerbations, and the development of resistance and adverse events. A review of macrolide treatment in respiratory diseases[36] suggested that treatment durations of at least 3 months are necessary to establish and maintain beneficial effects. This notion is supported by our Kaplan-Meier curves for the proportion of patients free of exacerbations, which continued to diverge beyond 3 months of treatment. We recommend a careful approach to the selection of patients for long-term azithromycin treatment. Patients who are selected should have had at least one exacerbation in the past year, have had no macrolide treatment for more than 3 months in the past 6 months, and be screened for non-tuberculous mycobacterial infection. Physicians should also take into account the evidence that resistance to macrolides in common respiratory pathogens such as *S pneumoniae* is increasing,[37] and that macrolide use is the most important driver of the emergence of macrolide resistance in patients.[34]

Contributors

CW, LJ, NK, TE, and DM participated in study conception and design. CW, LJ, NK, TE, CTo, DM, WF, CTu, and LS participated in data interpretation. CW, LJ, NK, TE, CTo, DM, CTu, and LS edited the report. CW and LJ participated in data analysis and writing of the report. CTo, WF, CTu, and LS participated in data collection. HH participated in study design, data analysis and interpretation, and writing and editing of the report. PS participated in data interpretation and editing of the report. TA participated in study design and editing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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