

Long-term Erythromycin Therapy Is Associated with Decreased Chronic Obstructive Pulmonary Disease Exacerbations

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Rationale: Frequent chronic obstructive pulmonary disease (COPD) exacerbations are a major cause of hospital admission and mortality and are associated with increased airway inflammation. Macrolides have airway antiinflammatory actions and may reduce the incidence of COPD exacerbations.

Objectives: To determine whether regular therapy with macrolides reduces exacerbation frequency.

Methods: We performed a randomized, double-blind, placebo-controlled study of erythromycin administered at 250 mg twice daily to patients with COPD over 12 months, with primary outcome variable being the number of moderate and/or severe exacerbations (treated with systemic steroids, treated with antibiotics, or hospitalized).

Measurements and Main Results: We randomized 109 outpatients: 69 (63%) males, 52 (48%) current smokers, mean (SD) age 67.2 (8.6) years, FEV₁ 1.32 (0.53) L, FEV₁% predicted 50 (18)%. Thirty-eight (35%) of the patients had three or more exacerbations in the year before recruitment, with no differences between treatment groups. There were a total of 206 moderate to severe exacerbations: 125 occurred in the placebo arm. Ten in the placebo group and nine in the macrolide group withdrew. Generalized linear modeling showed that the rate ratio for exacerbations for the macrolide-treated patients compared with placebo-treated patients was 0.648 (95% confidence interval: 0.489, 0.859; $P = 0.003$) and that these patients had shorter duration exacerbations compared with placebo. There were no differences between the macrolide and placebo arms in terms of stable FEV₁, sputum IL-6, IL-8, myeloperoxidase, bacterial flora, serum C-reactive protein, or serum IL-6 or in changes in these parameters from baseline to first exacerbation over the 1-year study period.

Conclusions: Macrolide therapy was associated with a significant reduction in exacerbations compared with placebo and may be useful in decreasing the excessive disease burden in this important patient population.

Clinical trial registered with www.clinicaltrials.gov (NCT 00147667)

Keywords: FEV₁; chronic obstructive pulmonary disease exacerbation; macrolide; exacerbation frequency

Patients with chronic obstructive pulmonary disease (COPD) are prone to frequent exacerbations that are a major cause of hospital admission, mortality, primary care visits, and impaired

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Frequent chronic obstructive pulmonary disease (COPD) exacerbations are a major cause of hospital admission and mortality and are associated with increased airway inflammation. Macrolides have airway antiinflammatory actions and may reduce the incidence of COPD exacerbations.

What This Study Adds to the Field

Macrolide therapy was associated with a significant reduction in COPD exacerbations compared with placebo and may be useful in decreasing the excessive disease burden in this patient population.

health status and have significant health economic consequences (1–3). Patients with frequent exacerbations have increased airway inflammation in the stable state (4) and a faster decline in lung function and thus COPD exacerbations affect disease progression, with the contribution of frequent exacerbations to FEV₁ decline being on the order of 25% of total decline (5). However, antiinflammatory therapy in COPD with steroids has only a relatively small effect on airway inflammation; there is evidence from the TORCH (TOwards a Revolution in COPD Health) Study, but not from other, smaller studies (6–11), that steroids slow disease progression.

Macrolides have both antibacterial and antiinflammatory activity (12–14). It has been suggested that the antiinflammatory activity is not related to the antibacterial action because the antiinflammatory effect is seen at low concentrations, below the minimal inhibitory concentration for airway bacteria (12). Human rhinovirus (HRV) is the commonest trigger of a COPD exacerbation (15); HRV infections account for the more severe COPD exacerbations (15) and macrolides may reduce airway cytokine production caused by HRV (16), thus reducing the susceptibility to exacerbation. Hence macrolides may reduce the frequency of COPD exacerbations, and thus disease progression as well. Macrolides are now used long term in conditions such as cystic fibrosis to reduce airway inflammation (17, 18).

We report in this article on a single-center, randomized, double-blind, placebo-controlled trial of a macrolide, erythromycin, in patients with moderate to severe COPD to test the hypothesis that regular therapy with macrolides reduces exacerbation frequency. Data from this study have been previously presented in abstract form at international meetings (19, 20).

METHODS

We recruited 115 patients with COPD from outpatient chest clinics of the London Chest Hospital (London, UK) and the Royal Free Hospital

(London, UK). Ethical permission for the study was obtained from St. Bartholomew's and the London Hospitals Trust as well as the Royal Free Hospital Trust Ethics committees.

Study Design

The study was a single-center, double-blind, randomized, placebo-controlled trial of erythromycin stearate (250 mg twice daily; Abbott Laboratories [Abbott Park, IL], supplied by DHP Clinical Trial Solutions [Powys, Wales, UK]). There was a 1-month run-in period followed by a 1-year treatment period. Coprimary outcome measures were exacerbation frequency and airway inflammation.

Subjects

Patients with COPD had influenza vaccination as recommended. All patients completed daily diary cards for changes in respiratory symptoms, and all patients were trained to report exacerbations to our research team, as soon as possible after onset of symptoms and before therapy was started as we have previously reported (15).

Inclusion and Exclusion Criteria

Patients were included in this study if they had moderate to severe COPD with FEV₁ between 30% and 70% predicted, FEV₁ reversibility of less than 15% and/or less than 200 ml to β_2 -agonists, were past or present cigarette smokers, and had no antibiotics or oral steroids during the run-in period. Patients were excluded if there was a history of asthma, bronchiectasis, neoplasia or other significant respiratory disease, unstable cardiac status (e.g., cardiac failure, prolonged QTc interval, cardiac arrhythmia), a history of macrolide allergy, or a history of hepatic impairment defined as abnormal liver function tests. Patients were excluded if they were taking drugs that could adversely interact with macrolides and for which therapeutic monitoring could not be undertaken. Most patients were taking inhaled steroids at recruitment. Over the study period no change in any therapy with antiinflammatory activity was allowed unless there was a clinical necessity, in which case the patient was then excluded from the study.

Recruitment and Run-in Period

The trial profile is shown in Figure 1. Patients were recruited if they fulfilled the inclusion criteria and were reviewed at the start of the run-in period when diary cards were provided as previously described (3). Patients were reviewed at the end of the run-in period, at the randomization visit. A run-in period was chosen so that patients would be free of exacerbation symptoms before baseline sampling. Because physiological changes associated with an exacerbation return to baseline in 70 to 74% of patients by about 4 weeks (19), a run-in period of 1 month was chosen. At recruitment the following were noted: baseline FEV₁, number of exacerbations in the previous 12 months, and age. Baseline samples of sputum and blood were also taken.

Randomization Visit

Figure 1 shows that 6 of the patients recruited could not be randomized; thus 109 patients were randomized in all. At the randomization visit, spirometry was measured and the number of exacerbations in the previous 12 months was noted. Computer-generated randomization numbers were stored in sealed envelopes. Placebo and erythromycin (250 mg) were concealed in identical capsules. Medication was randomized before commencement of the study by the hospital pharmacy, independently of trial staff. Randomization was taken in blocks of 10 (5 placebo, 5 erythromycin) and patients were automatically dispensed the next allocated treatment (containing either erythromycin 250 mg twice daily or placebo twice daily for 3 mo and repeated at each clinic visit up to 1 yr). Unblinding occurred after data entry.

Follow-up of Patients, Stable Samples, and Withdrawal from the Study

Spirometry, sputum testing for bacteria, and spontaneous sputum and blood testing for inflammatory markers were performed at each follow-up visit. At these visits, diary cards were reviewed for exacerbations. Patients were also instructed to report to clinic within 48 hours of the onset of respiratory symptoms for detection of exacerbations as in our

previous work (15). All initial measures were repeated at the final visit at 12 months. For purposes of analysis, a patient was said to have stable COPD if the patient was asymptomatic. A sample taken at this time was called a *stable sample*. All patients were followed up even if they left the study and even if they prematurely discontinued study treatments and returned to cohort follow-up. Deaths were monitored for the 1-year duration of the study for all patients.

We instructed patients and their primary care physicians that any exacerbations deemed to require antibiotics should receive penicillin or ciprofloxacin. If patients were admitted to hospital they were required to call a member of the study team, who would then contact the clinical team and convey the preceding instructions. If in spite of this the clinical team concluded that the use of a macrolide or quinolone other than ciprofloxacin was indicated, then the patient was withdrawn from the study. Patients were also withdrawn if they developed any evidence of macrolide toxicity.

Definition and Treatment of Exacerbations

A moderate exacerbation was defined as a sustained worsening of baseline respiratory symptoms for at least 2 days that required treatment with oral corticosteroids (prednisolone) and/or antibiotics, and a severe exacerbation was defined by the requirement for admission to hospital. Information about exacerbations was collected during clinic visits, and any patient experiencing worsening respiratory symptoms was instructed to contact the investigator immediately and to report to the study clinic as soon as possible as previously described (15, 21). Exacerbations were adjudicated in a blinded manner by one of the authors who was not involved in data collection during the course of the study.

The date of onset of an exacerbation was defined as the day of the first recorded symptom of that exacerbation and the end date of the exacerbation was defined as the day of disappearance of all symptoms associated with the exacerbation for at least two consecutive days. The duration of the exacerbation was defined as the number of days from onset to end. The procedure for management of an exacerbation when patients had deteriorating respiratory symptoms has been previously described (15). Exacerbation frequency was defined as the number of moderate to severe exacerbations over the 12-month follow-up period. Primary compliance data were collected from patient-completed diary card entries, which were checked against pill counts, and side effects were also recorded on diary cards.

Laboratory Analysis of Blood and Sputum Samples

Serum and sputum samples were obtained at each visit. Serum samples were analyzed for IL-6 by ELISA (R&D Systems, Abingdon, UK). Serum C-reactive protein (CRP) was measured with an Olympus luminometric analyzer (Olympus Life and Material Science Europa GmbH, Hamburg, Germany). Sputum samples were sent for identification and sensitivity testing according to our previously published methodology and according to British Society for Antimicrobial Chemotherapy guidelines (22, 23). Sputum levels of IL-6, IL-8, and myeloperoxidase (MPO; EMD Biosciences, San Diego, CA) were determined by ELISA as previously described (22).

Adverse Events Monitoring

On recruitment all patients had an ECG, liver and renal function, and complete blood count measurements and if patients were taking theophyllines then theophylline levels were measured. ECGs were repeated at screening and at 1 and 3 months to check the QTc interval. If the QTc interval was abnormal the patient would be withdrawn. ECGs were performed thereafter only if a patient's symptoms were suggestive of unstable cardiac disease. Liver function testing of patients was repeated on follow-up visits and theophylline levels of all patients taking theophyllines were checked. Patients also recorded on daily record cards symptoms that they believed were related to therapy, for example, upper gastrointestinal, lower gastrointestinal, rash, and so on, and these were reviewed at the clinic. If a patient had an adverse event that was thought to be drug related and that did not resolve, then the patient was withdrawn from the study. There was no routine screening of hearing as this was not thought to be a significant side effect at this dose of macrolide (24–26).

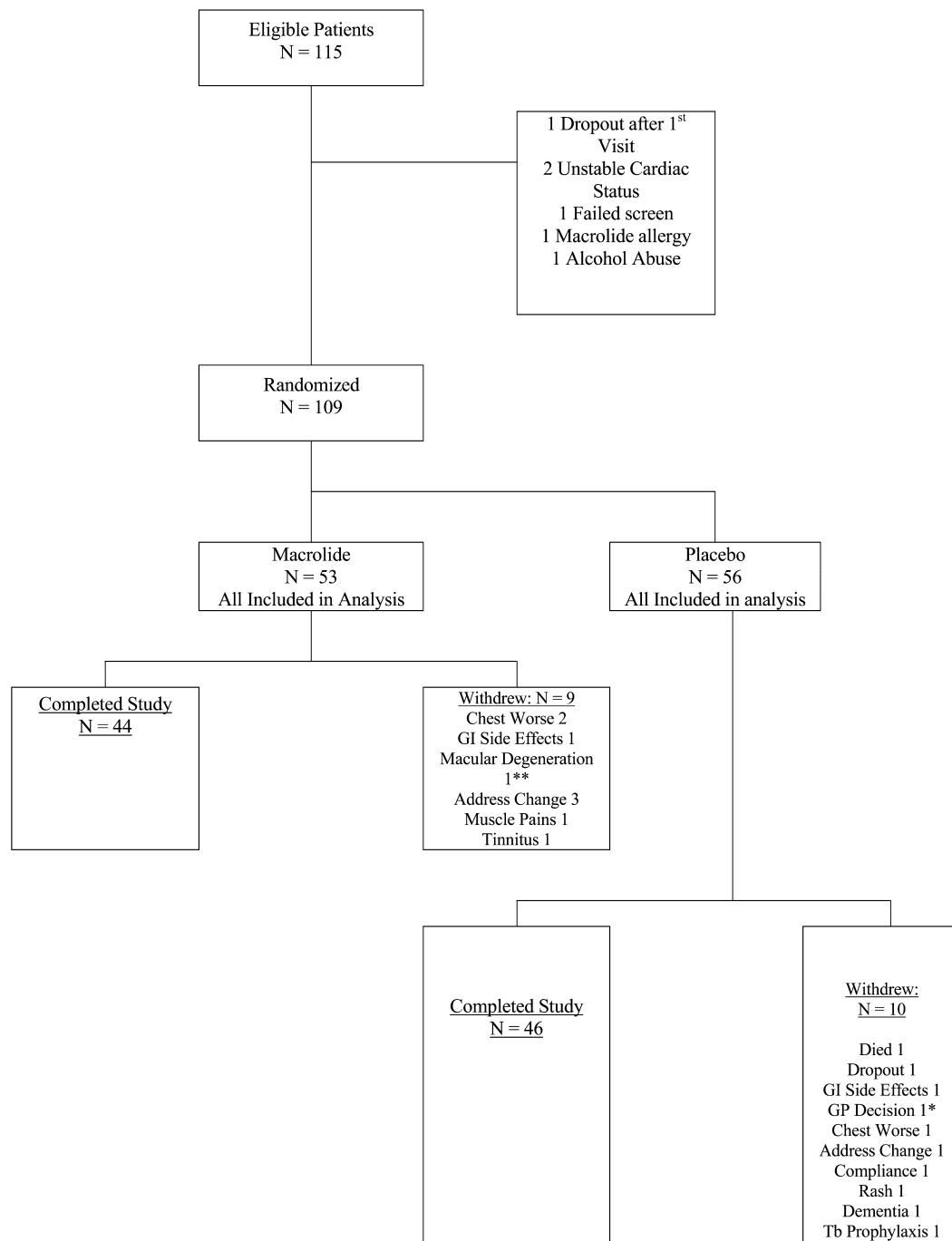


Figure 1. CONSORT diagram for flow of patients through the study. There were 9 dropouts in the macrolide arm and 10 in the placebo arm. In all, 90 patients completed the study on treatment. All patients were used in the intent-to-treat analysis.

Statistical Analysis

From our previous work on the London COPD cohort, we have found that the average exacerbation frequency is three exacerbations per patient per year (3). To reduce exacerbation frequency from 3 per year to 1.5 per year with 5% significance and 90% power, 58 patients had to be studied in each of the active and placebo groups. However, we have observed an average dropout rate of 15% per year in our cohort. Hence a target of 68 patients was required in each arm of the study and so we expected to recruit 136 patients with COPD in total. Statistical analysis was performed after unblinding.

Data for continuous variables was expressed as means (standard deviation [SD], standard error [SE], or 95% confidence interval [95% CI]) and discrete data were summarized as number (percent). Associations were considered statistically significant at the 5% level.

To determine the independent effects of the drug on the frequency of moderate to severe COPD exacerbations, multivariate analysis was

performed with the number of moderate to severe exacerbations as the outcome variable, using a generalized linear model for a Poisson distribution with log of time on treatment as an offset variable and covariates of baseline smoking status, sex, disease severity (percentage of predicted FEV₁ at baseline), number of exacerbations in the 12 months before screening (dichotomized as frequent or infrequent), and age. Time to first exacerbation between the two treatment arms was examined by Kaplan-Meier survival analysis, using all patients, and statistical significance was determined by log-rank test.

Exacerbation duration between the placebo and macrolide arms of the study was analyzed with a generalized linear model for Poisson distribution. For each exacerbation, treatment was binary-coded as with or without oral steroids. The model allowed for oral steroid treatment of each exacerbation, arm of the study, and baseline covariates of smoking status, number of exacerbations in the 12 months before screening (dichotomized as frequent or infrequent, i.e., baseline

exacerbation rate), age, and disease severity (percentage of predicted FEV₁ at baseline) with log of time on treatment as offset variable.

Serial stable FEV₁, serum CRP, serum IL-6, sputum IL-6, sputum IL-8, and sputum MPO data over the year were compared by linear mixed models analysis with visit number as the repeated measure and the respective physiological or inflammatory marker as dependent variable. The comparison was performed between treatments with covariates of baseline exacerbation rate, baseline smoking status, disease severity, age, and sex. A similar model was used to examine differences between macrolide and placebo for changes between baseline parameters and first exacerbation.

All analyses used the intent-to-treat population, defined as all randomized patients who received at least one dose of study medication. The study was designed to show the superiority of either arm and used a two-sided test at the 5% level of significance. Analyses were performed with SPSS version 12 for Windows (SPSS, Chicago, IL), apart from the generalized linear modeling and survival analyses, which were performed with SPSS version 15.

RESULTS

Recruitment and Baseline Data

Although our sample size calculation required that we recruit a total of 136 patients, we recruited only 115 patients to the study before the preassigned date of study closure of March 2006. Figure 1 shows that there were an equivalent number of withdrawals in each arm of the study and in all 90 patients completed the study. Median compliance was 99%. The 109 patients had a mean age 67.2 (8.6) years, with 63% males. The mean FEV₁ was 1.32 (0.53) L, FVC 2.67 (0.87) L, and FEV₁% 50.0 (18.0)%. Thirty-eight patients had three or more exacerbations in the year before recruitment. Table 1 shows that there was no difference between the two treatment groups in any of these parameters.

All patients were current smokers (n = 52) or ex-smokers and had a mean (SD) duration of 50.5 (36.1) and 52.8 (31.7) pack-years of smoking in the placebo and macrolide groups, respectively. Twelve patients were taking oral theophylline

tablets (4 in the macrolide group). Table 2 shows that there was no difference in the number of patients taking inhaled steroids between the two arms of the study.

The number of patients attending follow-up visits at 1, 3, 6, 9, and 12 months, respectively, was as follows: 83, 85, 92, 85, and 89 (patient 90 attended for follow-up at more than 4 wk after the end of the study; diary cards were collected but the patient was not sampled).

Exacerbation Frequency

There were a total of 206 moderate to severe exacerbations, of which 125 occurred in the placebo arm and 81 in the macrolide group. This shift of the exacerbation frequency curve to the left (less moderate to severe exacerbations) in the macrolide group is shown in Figure 2. There were 14 (11.2%) hospitalizations for COPD exacerbation in the placebo group and 6 (7.4%) in the macrolide group. There was a median (interquartile range) exacerbation frequency of 2 (0.25, 3.75) in the placebo arm and 1.00 (0.00, 2.00) in the macrolide arm of the study ($P = 0.006$; Mann-Whitney test). Table 2 shows that the exacerbation frequency was significantly reduced in the macrolide arm of the study, with a rate ratio of a moderate/severe exacerbation being 0.648 compared with placebo, and that exacerbations occurring during the study were more frequent in patients with a history of frequent exacerbations at baseline or lower FEV₁% predicted at recruitment. Sex and smoking status did not affect exacerbation frequency. Kaplan-Meier survival analysis showed that the median time to the first exacerbation in the macrolide arm was 271 days versus 89 days in the placebo arm ($P = 0.020$; log-rank test) (Figure 3).

Exacerbation Duration and Inflammation at Exacerbation

The duration of the exacerbation could be calculated for a total of 168 exacerbations (97 placebo, 71 macrolide). Median duration of exacerbations in the placebo arm was 13 (6–24) days, and in the macrolide arm of the study it was 9 (6–14) days

TABLE 1. BASELINE VARIABLES FOR THE TWO TREATMENT GROUPS

Continuous Variable	Drug					
	Placebo			Macrolide		
	n	Mean	SD	n	Mean	SD
Age, yr	56	67.79	9.08	53	66.54	8.10
FEV ₁ , L	56	1.36	0.55	53	1.27	0.51
FEV ₁ , % predicted	56	50.55	18.87	53	49.25	17.30
FVC, L	56	2.71	0.97	53	2.63	0.79
FEV ₁ /FVC, %	56	50.90	13.52	53	48.92	12.84
Serum CRP, mg/L	54	7.72	7.33	52	7.97	6.22
Serum IL-6, pg/ml	54	6.56	16.62	51	5.74	7.05
Sputum IL-6, pg/ml	50	188.34	169.28	38	171.37	165.91
Sputum IL-8, pg/ml	50	2,806.00	1,348.57	39	3,078.09	1,302.08
Sputum MPO, ng/ml	47	9.95	12.24	39	13.18	18.50
Discrete Variable	n	%		n	%	
Smoker	25	45		27	51	
Male sex	36	64		33	62	
Three or more exacerbations in the year before recruitment	19	34		19	36	
Inhaled steroids	44	77		41	77	
LABA	34	61		35	66	
LAMA	21	38		15	28	
Theophylline	8	14		4	7.5	

Definition of abbreviations: CRP = C-reactive protein; LABA = long-acting bronchodilator; LAMA = long-acting antimuscarinic; MPO = myeloperoxidase.

n = 109 patients with COPD ($P > 0.05$ for all comparisons between placebo and macrolide groups). Percentages are shown to two significant figures.

TABLE 2. MULTIVARIATE ANALYSIS BY INTENT TO TREAT WITH EXACERBATION FREQUENCY (OUTCOME VARIABLE) IN 109 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE TREATED WITH MACROLIDE OR PLACEBO

Parameter	Rate Ratio	95% CI		P Value
		Lower	Upper	
Macrolide	0.648	0.489	0.859	0.003
Frequent exacerbations at baseline	2.679	2.008	3.575	<0.001
Current smoker	1.056	0.789	1.414	0.715
Male sex	0.884	0.660	1.184	0.407
	Regression Coefficient			
Age, yr	-0.015	-0.032	0.002	0.086
FEV ₁ % at baseline	-0.008	-0.016	0.000	0.046

Definition of abbreviation: 95% CI = 95% confidence interval. Rate ratios are shown for binary variables and regression coefficients (B) are shown for continuous variables with 95% confidence intervals. See text for details.

($P = 0.036$; Mann-Whitney test). Figure 4 illustrates this difference by showing that there was a greater proportion of short-duration exacerbations in patients taking macrolide compared with those taking placebo. For example, 63% of exacerbations had ended by Day 10 in the macrolide arm as opposed to 40% in the placebo arm. Poisson regression with duration of exacerbation as outcome variable revealed that patients in the macrolide arm were likely to have a shorter duration exacerbation (regression coefficient [B] = -0.286 , $P < 0.001$). Other significant factors in the regression were a history of three or more exacerbations in the year before recruitment (B = -0.301 , $P < 0.001$) and oral steroid treatment at exacerbation (B = 0.177 , $P < 0.001$).

There was no difference between drug and placebo arms in terms of changes at first exacerbation in FEV₁, serum CRP, serum IL-6, or sputum inflammatory markers. Details are shown in the online supplement.

Stable Spirometry and Inflammatory Markers over 1 Year

Stable data for months 0, 1, 3, 6, 9, and 12 were analyzed for trends over time for FEV₁ and serum and sputum inflammatory markers. Table 3 shows the data for 0 and 12 months only. Linear mixed models analysis for the sequential data over the year showed no significant change in any parameter with respect to time. The P values for this analysis are shown in Table 3.

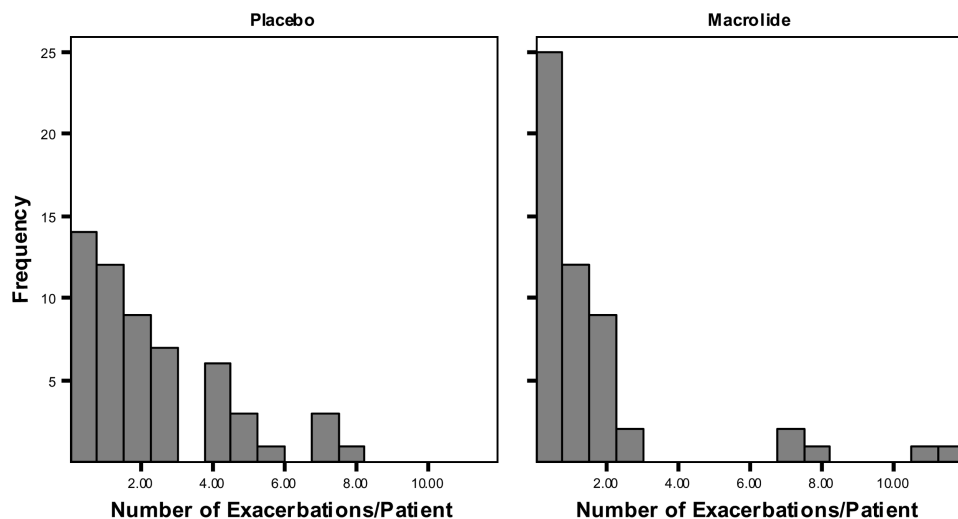


Figure 2. Distribution of exacerbation frequencies in the two arms of the study. Exacerbations were less frequent in the macrolide arm ($P = 0.003$).

Bacteriology

Three hundred and thirty-nine sputum samples were taken for analysis for bacterial species from patients who spontaneously produced sputum. Of these, 73 were at exacerbation and the rest at baseline or follow-up. All *Haemophilus influenzae* were resistant or assumed constitutionally resistant to erythromycin. Detection of *H. influenzae* was positive in 27% stable samples and in 40% of exacerbation samples, and the corresponding distribution for *Streptococcus pneumoniae* was 7 and 10%, respectively. There was no difference in detection rate for any organism between the two arms of the study at any of the follow-up time points ($P > 0.05$ in all cases).

Sensitivity testing showed that at baseline 69 patients (placebo [P] = 39; macrolide [M] = 30) produced sputum samples, of which 33 showed no significant growth. Of those in which a bacterial pathogen was found there were *H. influenzae* (22, all resistant [P = 12, M = 10]), *S. pneumoniae* (6, all sensitive [P = 5, M = 1]), and *Mycobacterium catarrhalis* (3, all sensitive [P = 2, M = 1]). At the 12-month follow-up visit there were 43 sputum samples (P = 20, M = 23), with no significant growth in 26. Of those in which pathogens were detected there were *H. influenzae* (4 [P = 3, M = 1]), *S. pneumoniae* (3 [P = 2, all sensitive; M = 1, resistant]), and *M. catarrhalis* (3, two sensitive and sensitivity unknown in one [P = 2]).

Adverse Events Profile

Table 4 shows that there was no significant difference in side effects between patients in the two arms of the study and that the frequency of side effects was low in both arms of the study. In some cases more than one side effect occurred in the same patient, for example, the occurrence of an upper gastrointestinal symptom in a patient who also had tinnitus (classified as “other” in Table 4). Of the 12 patients taking theophyllines, no serum theophylline levels above the therapeutic range were detected during the study.

DISCUSSION

This is the first 12-month randomized controlled study of the effect of macrolide therapy in COPD. The results show a significant effect of low-dose macrolide therapy, reducing exacerbation frequency and severity in patients with moderate to severe COPD. The treatment was well tolerated over the 1-year study period. The study groups were similar with respect to age, FEV₁%, sex, sputum inflammatory markers, and exacerbation

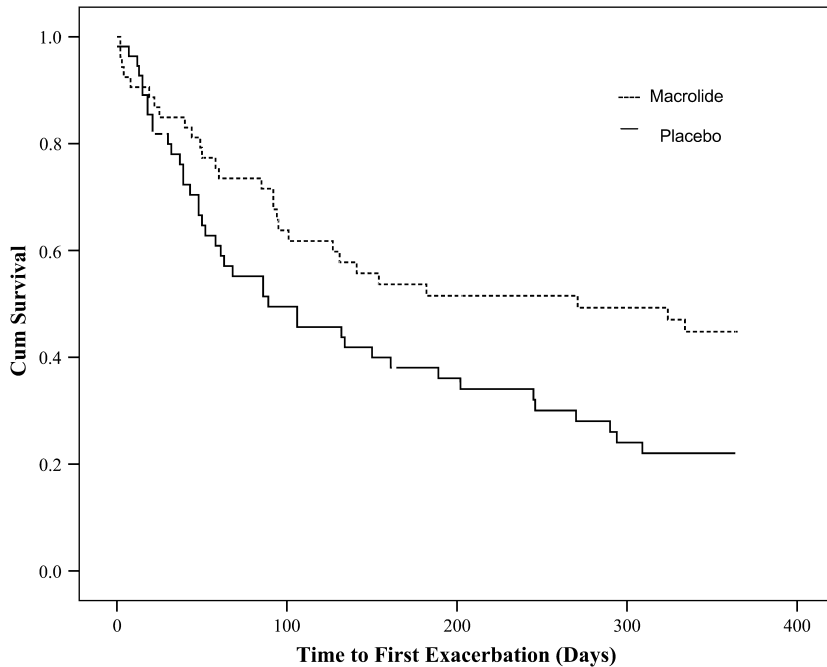


Figure 3. Kaplan-Meier curves showing the proportion of patients without an exacerbation (Cum Survival axis) versus time to the first exacerbation between macrolide and placebo arms of the study. Patients in the macrolide arm were less likely to have a first exacerbation than those in the placebo arm ($P = 0.02$).

frequency in the year before recruitment. Despite the fall in exacerbation frequency, we found no differences between the two arms of the study in FEV₁ decline, airway or sputum inflammatory markers, or bacteria isolated over the 12-month study period. The duration of the exacerbations in the macrolide arm of the study was significantly shorter than in the placebo arm.

Oral macrolides have been shown to affect outcomes in two diseases that involve chronic airway obstruction: diffuse panbronchiolitis and cystic fibrosis (CF). In diffuse panbronchiolitis, for which erythromycin has been the most commonly used drug, there has been a highly significant improvement in survival (27) and symptoms (28–30). Studies in CF have used mostly azithromycin and found improvement in morbidity, with the randomized controlled trials all showing a significant decrease in CF exacerbations in the macrolide arm in both children (18, 31, 32) and young adults (17). We and others have previously shown that respiratory viruses, mainly rhinoviruses, are associated with up to 50% of COPD exacerbations (15, 33–35). In addition, erythromycin had been shown to decrease

the inflammatory response to rhinovirus *in vitro* (16). Thus, for this reason, we chose to study erythromycin in the patients described here. We have found that erythromycin use was associated with a 35% fall in the rate ratio of moderate to severe exacerbations compared with the placebo arm patients. Our results are also similar to those of an open label study of 109 patients with COPD from Suzuki and colleagues, who found that erythromycin use was associated with a decrease in exacerbation frequency (36). The rate ratio for a moderate to severe exacerbation of COPD in the macrolide arm of our study was of similar magnitude to that of exacerbations in the azithromycin-treated arm in children with cystic fibrosis (32).

Previous studies have shown that inhaled steroid use is associated with about a 25% reduction in the mean exacerbation frequency in patients with moderate to severe COPD (6, 37). There was no statistically significant difference between the macrolide and placebo arms of our study in inhaled steroid use or dosage. Nevertheless, we found a significant reduction in exacerbation rate in the macrolide arm compared with the placebo arm. Our data would appear to suggest that the effect

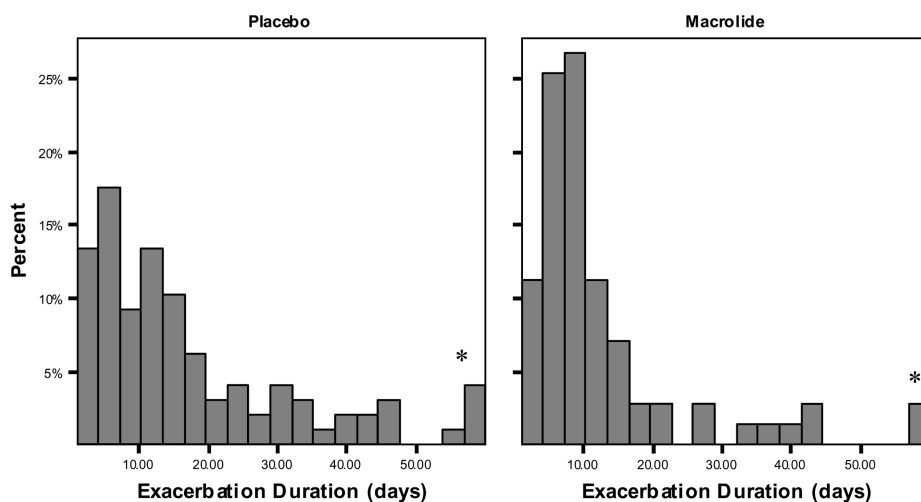


Figure 4. Duration of exacerbations between macrolide and placebo groups during the study. Patients in the macrolide arm were more likely to have shorter duration exacerbations ($P \leq 0.001$). The far right column (*) in each panel represents durations greater than or equal to 60 days. See text for explanation.

TABLE 3. ANALYSIS OF STABLE SPIROMETRY AND INFLAMMATORY MARKERS OVER 1 YEAR

Group	Time	FEV ₁ (L)	Serum IL-6 (pg/ml)	Serum CRP (mg/L)	Sputum IL-6 (pg/ml)	Sputum IL-8 (pg/ml)	Sputum MPO (ng/ml)
Placebo	Baseline						
	n	56	54	54	50	50	47
	Mean	1.33	6.54	7.63	195	2,884	10.2
	95% CI	1.19–1.47	3.08–9.99	5.76–9.50	147–242	2,511–3,257	5.61–14.8
	12 mo						
	n	45	40	42	31	31	30
Macrolide	Baseline						
	n	53	51	52	38	39	39
	Mean	1.25	5.66	7.75	174	3,095	13.3
	95% CI	1.11–1.39	2.11–9.21	5.89–9.64	120–228	2,678–3,514	8.3–18.2
	12 mo						
	n	44	38	41	25	25	25
P value (treatment × time)	Mean	1.13	6.09	6.47	128	3,138	16.1
	95% CI	0.96–1.30	1.53–10.66	2.98–9.96	63–194	2,576–3,699	6.3–25.8
	Mean	0.966	0.884	0.812	0.514	0.551	0.201
	95% CI						
	Mean						
	95% CI						

Definition of abbreviations: CRP = C-reactive protein; MPO = myeloperoxidase; 95% CI = 95% confidence interval.

Shown are data only for the baseline visit (visit 0) and final (12 mo) visit. The estimated means are displayed together with the 95% confidence intervals. The *P* value for interaction between time and treatment over the 12-month period is shown for each variable. The table reveals that there is no difference in trend between the two arms of the study for the parameters shown. (Statistical modeling is by linear mixed models for visits 0, 1, 3, 6, 9, and 12; see text for details.) Note that the means shown here are means estimated from the multivariate model used for this analysis. Thus they differ slightly from the mean baselines shown in Table 1.

of the macrolide, erythromycin, occurred on top of any effect that inhaled steroid may have had on reducing exacerbation frequency. The mechanism by which steroids affect exacerbations may involve action at the nuclear level, but the precise mechanism by which macrolides affect exacerbation frequency is unknown. However, our study was not designed to test the hypothesis of an additive effect of macrolides on inhaled steroid therapy.

We found no difference in FEV₁ between the two arms of the study over the 1-year period. Previous studies of lung function changes in CF have been equivocal, with macrolide use favoring small differences in three studies (17, 18, 31) but not in a fourth (32). The study by Wolter and colleagues found no evidence of a decline in FEV₁ in the macrolide arm but a 3.6% decline in FEV₁% in the placebo arm (17). Apart from the TORCH Study (38), most of the more recent long-term studies of COPD have not found significant differences between interventional and placebo arms in FEV₁ decline (6, 8, 37, 38). In a 4-year study, we showed that an exacerbation frequency greater than about three per year is associated with a greater rate of FEV₁ decline by about 25% (5), which has been supported by data from the Lung Health Study (39). Thus it can be hypothesized that if exacerbations decreased in the macrolide arm, there would be a corresponding decrease in the rate of FEV₁ decline. However, our study was not powered to detect such a difference in FEV₁ decline.

We have previously shown that lower airway bacterial colonization in patients with COPD is related to exacerbation frequency (22). There is legitimate concern regarding the development of resistance with any trial of long-term antibiotics. However, in this study the microbiological profile of sputum was not influenced by the use of erythromycin. Only one case of erythromycin resistance occurred in the study in the macrolide arm at 12 months, but we do not make any definitive inference from this result because of the small size of our study. Similar results have been reported in adults and children with CF (17, 18, 32), although macrolide-resistant *S. aureus* has also been found in these patients (40).

In vitro studies of the macrolide erythromycin have shown a reduction in the inflammatory response to human rhinovirus (16), and Jang and colleagues have shown that clarithromycin

is associated with a decrease in rhinovirus titer in infected A549 pulmonary epithelial cells (41). There is also evidence that macrolides decrease neutrophil activity through lowered oxidant production (42), decreased bacterial adhesion (30), increased bactericidal activity (13, 43), and antichlamydial activity (44). There are few data on systemic inflammatory markers in macrolide studies of patients with CF, with only one study showing a significant fall in CRP in adults with CF when treated with macrolides (17). We found that inflammatory markers measured in sputum and blood remained stable throughout the 12-month period in both arms.

Sputum inflammatory markers may show significant variability and it is possible that by using induced sputum samples, this variability may have been reduced, although one study has shown consistency between levels of inflammatory markers in spontaneous and induced sputum (4). However, previous studies of inhaled corticosteroids on sputum markers have not shown effects on reducing inflammation (7), although studies of the effect of inhaled corticosteroid therapy on airway biopsies have shown some reduction in airway inflammatory cells (10, 11, 45). Thus adequately powered airway biopsy studies of the effects of long-term macrolides on airway inflammation in COPD are now required.

We found that exacerbations in the macrolide arm were shorter in duration and therefore perhaps less severe (21), compared with the placebo arm, even after allowance for oral steroid treatment at exacerbation. There was also no difference in inflammatory markers at exacerbation for the two treatment

TABLE 4. NUMBER OF PATIENTS WITH ADVERSE EVENTS DURING THE 1-YEAR STUDY

Side Effect	Placebo	Macrolide
Upper GI	5	5
Lower GI	3	3
Rash	2	3
Other	2	3

Definition of abbreviation: GI = gastrointestinal.

P > 0.05 in all case for comparison between placebo (*n* = 56) and macrolide (*n* = 53). Upper GI effects were nausea, vomiting or dyspepsia. Lower GI effects were diarrhea or cramps.

arms. This is in keeping with our previous findings that exacerbation clinical severity is not closely related to the degree of inflammatory change at exacerbation (4).

The drug was well tolerated, with similar adverse events in both groups, and these results were similar to those described in other long-term studies of CF (17, 32). All patients at recruitment had normal QTc intervals as determined by electrocardiography. There were no treatment-emergent changes in QTc interval or liver function tests. Median compliance was high during the study, at 99%, although compliance was assessed by counting tablets at every visit and may have been overestimated. Although no significant difference was found between the two arms of the study in terms of inflammatory markers and bacterial agents, it is important to note that our study was not powered to detect a difference in these parameters. A further limitation of our study is that it would have been useful to correlate changes observed over the year with quality of life data, which were not systematically measured during the study.

In conclusion, we have shown that the macrolide erythromycin, at a dosage of 250 mg twice daily, is associated with a significant reduction in moderate to severe exacerbations in patients with moderate to severe COPD. There was no corresponding effect on FEV₁ or on airway or systemic inflammatory markers. There was a statistically significant decrease in exacerbation duration associated with macrolide use. Macrolides have a role in COPD and may be used to augment therapy in patients with moderate to severe COPD.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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