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Azithromycin for Prevention of Exacerbations of COPD

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Abstract

BACKGROUND—Acute exacerbations adversely affect patients with chronic obstructive pulmonary disease (COPD). Macrolide antibiotics benefit patients with a variety of inflammatory airway diseases.

METHODS—We performed a randomized trial to determine whether azithromycin decreased the frequency of exacerbations in participants with COPD who had an increased risk of exacerbations but no hearing impairment, resting tachycardia, or apparent risk of prolongation of the corrected QT interval.

RESULTS—A total of 1577 subjects were screened; 1142 (72%) were randomly assigned to receive azithromycin, at a dose of 250 mg daily (570 participants), or placebo (572 participants) for 1 year in addition to their usual care. The rate of 1-year follow-up was 89% in the azithromycin group and 90% in the placebo group. The median time to the first exacerbation was 266 days (95% confidence interval [CI], 227 to 313) among participants receiving azithromycin, as compared with 174 days (95% CI, 143 to 215) among participants receiving placebo ($P<0.001$). The frequency of exacerbations was 1.48 exacerbations per patient-year in the azithromycin group, as compared with 1.83 per patient-year in the placebo group ($P=0.01$), and the hazard ratio for having an acute exacerbation of COPD per patient-year in the azithromycin group was 0.73 (95% CI, 0.63 to 0.84; $P<0.001$). The scores on the St. George's Respiratory Questionnaire (on a scale of 0 to 100, with lower scores indicating better functioning) improved more in the azithromycin group than in the placebo group (a mean $[\pm\text{SD}]$ decrease of 2.8 ± 12.8 vs. 0.6 ± 11.4 , $P=0.004$); the percentage of participants with more than the minimal clinically important difference of -4 units was 43% in the azithromycin group, as compared with 36% in the placebo group ($P=0.03$). Hearing decrements were more common in the azithromycin group than in the placebo group (25% vs. 20%, $P=0.04$).

CONCLUSIONS—Among selected subjects with COPD, azithromycin taken daily for 1 year, when added to usual treatment, decreased the frequency of exacerbations and improved quality of life but caused hearing decrements in a small percentage of subjects. Although this intervention could change microbial resistance patterns, the effect of this change is not known. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT00325897.)

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Acute exacerbations of chronic obstructive pulmonary disease (COPD) result in frequent visits to physicians' offices and emergency rooms and numerous hospitalizations and days lost from work; they also account for a substantial percentage of the cost of treating COPD.^{1–5} Patients who have acute exacerbations of COPD, as compared with patients with COPD who do not have acute exacerbations, have an increased risk of death, a more rapid decline in lung function, and reduced quality of life.^{6–11} Although inhaled glucocorticoids, long-acting beta₂-agonists, and long-acting muscarinic antagonists reduce the frequency of acute exacerbations of COPD,^{12–24} patients receiving all three of these medications may still have as many as 1.4 acute exacerbations, on average, each year.²³

Macrolide antibiotics have immunomodulatory, antiinflammatory, and antibacterial effects.²⁵ Seven small studies that tested whether macrolides decrease the frequency of acute exacerbations of COPD reported conflicting results.^{26–32} Accordingly, we conducted a large, randomized trial to test the hypothesis that azithromycin decreases the frequency of acute exacerbations of COPD when added to the usual care of these patients.

METHODS

STUDY DESIGN AND OVERSIGHT

We used a prospective, parallel-group, placebo-controlled design. Participants were randomly assigned, in a 1:1 ratio, to receive azithromycin, at a dose of 250 mg orally, or an identical-appearing placebo, once daily. Participants were recruited from 17 sites associated with 12 academic health centers in the United States. Written informed consent was obtained from all participants.

The study was approved by the institutional review board at each participating institution. The protocol was designed by the first author and was modified on the basis of input from the remaining authors. The complete protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The data were gathered by study personnel at each participating site, overseen by one of the authors at each site. The data were analyzed by the second author, who is a statistician, together with the first author. All the authors participated in interpreting the data. The first and final drafts of the manuscript were written by the first author and revised on the basis of input from the other authors and from members of the data and safety monitoring committee. All the authors made the decision to submit the manuscript for publication. There were no confidentiality agreements with the sponsor. The study drugs (both azithromycin and placebo) were purchased by the investigators. All the authors assume responsibility for the data and analyses and vouch for the fidelity of the study to the protocol.

STUDY PARTICIPANTS

Eligible participants were at least 40 years of age, had a clinical diagnosis of COPD (defined as having a smoking history of at least 10 pack-years, a ratio of postbronchodilator forced expiratory volume in 1 second [FEV₁] to forced vital capacity of <70%, and a postbronchodilator FEV₁ of <80% of the predicted value), were either using continuous supplemental oxygen or had received systemic glucocorticoids within the previous year, had gone to an emergency room or had been hospitalized for an acute exacerbation of COPD,¹⁹ and had not had an acute exacerbation of COPD for at least 4 weeks before enrollment.

Exclusion criteria were asthma, a resting heart rate greater than 100 beats per minute, a prolonged corrected QT (QTc) interval (>450 msec), the use of medications that prolong the QTc interval or are associated with torsades de pointes (with the exception of amiodarone),³³ and hearing impairment documented by audiometric testing.

OUTCOMES

The primary outcome was the time to the first acute exacerbation of COPD, with acute exacerbation of COPD defined as “a complex of respiratory symptoms (increased or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics or systemic steroids.”¹⁹ At each clinic visit and telephone contact, study personnel determined whether an acute exacerbation of COPD had occurred in the previous month. The date of each acute exacerbation was taken as the date treatment was prescribed.

Secondary outcomes included quality of life, nasopharyngeal colonization with selected respiratory pathogens (i.e., *Staphylococcus aureus*, *Streptococcus pneumoniae*, haemophilus species, and moraxella species), and adherence to taking the study drug as prescribed. The St. George’s Respiratory Questionnaire (SGRQ, in which scores range from 0 to 100, with lower scores indicating better functioning) and the Medical Outcomes Study 36-Item 691 Short-Form Health Survey (SF-36) were administered at the time of enrollment and at study months 6 and 12. The minimal clinically important difference in the SGRQ score was considered to be –4 units, and the percentage of patients with a change of at least 4 units from the time of enrollment was a prespecified end point.³⁴ Deep nasopharyngeal swabs were obtained at the time of enrollment and every 3 months thereafter, and selected respiratory pathogens were assessed for resistance to macrolides. Adherence to the study drug was assessed at each clinic visit by means of pill counts performed by the staff. Hearing was assessed by means of audiometry at the time of enrollment and at 3 and 12 months, or whenever a patient reported worsening hearing or tinnitus.

STATISTICAL ANALYSIS

We estimated that with enrollment of 1130 subjects, the study would have 90% power to show a significant difference between the two groups in the time to the first acute exacerbation of COPD, assuming that 50% of the participants in the control group¹⁹ and 40% in the azithromycin group²⁵ would have an acute exacerbation, that the rate of nonadherence would be 20%, and that 6% of participants would die or be lost to follow-up during the study (extrapolated from Niewoehner et al.¹⁹), with a two-sided type I error of 0.05.

The groups were compared with the use of an intention-to-treat survival analysis. The primary analysis was based on a log-rank test of the difference between the two treatment groups in the time to the first exacerbation, with no adjustments for baseline covariates. A Cox proportional-hazards model was used to adjust for differences in prespecified, prerandomization factors that might predict the risk of acute exacerbations of COPD. Bootstrap methods were used to compute confidence intervals for median times to the first exacerbation and for the difference in median times between the two groups.³⁵ The rates of acute exacerbations of COPD were determined by dividing the number of acute exacerbations by the person-years of follow-up and were compared with the use of both Poisson and negative binomial analyses.

The data and safety monitoring board met approximately every 6 months and had the authority to stop the study prematurely on the basis of any of the interim analyses and on the basis of calculations of conditional power derived from a futility analysis supplied at each analysis. Accordingly, the data were analyzed with the use of group sequential testing³⁶ that allowed “spending” a little of the alpha at each interim analysis such that, at the end of the study, the total type I error did not exceed 0.05.

RESULTS

STUDY PARTICIPANTS

The screening, randomization, and follow-up of patients are shown in Figure 1. The first site started enrolling participants in March 2006, and the last patient finished the 1-year follow-up assessment on June 30, 2010. The characteristics of the participants at the time of enrollment are summarized in Table 1. All reported results were prespecified.

PRIMARY OUTCOME

A life-table analysis showed that the risk of acute exacerbations of COPD was reduced among participants receiving azithromycin ($P<0.001$) (Fig. 2). The median time to the first acute exacerbation of COPD was 266 days (95% confidence interval [CI], 227 to 313) in participants receiving azithromycin, as compared with 174 days (95% CI, 143 to 215) in participants receiving placebo ($P<0.001$). The hazard ratio of having an acute exacerbation of COPD per patient-year in the azithromycin group as compared with the placebo group was 0.73 (95% CI, 0.63 to 0.84; $P<0.001$). These differences remained significant after adjustment with the use of Cox regression for differences in sex, FEV₁, age, smoking status, and study center. The rates of acute exacerbations of COPD differed according to center, but the hazard ratio for the time to the first acute exacerbation of COPD, stratified according to center, was 0.71 (95% CI, 0.61 to 0.83; $P<0.001$).

A total of 1641 acute exacerbations of COPD occurred during the study — 741 among the 558 participants who received at least one dose of azithromycin and 900 among the 559 who received at least one dose of placebo, and the rates of acute exacerbations of COPD per patient-year were 1.48 and 1.83, respectively ($P=0.01$; rate ratio from negative binomial analysis, 0.83; 95% CI, 0.72 to 0.95). The frequency of acute exacerbations was lower among participants receiving azithromycin than among those receiving placebo regardless of the rate of acute exacerbations per patient-year ($P=0.008$ by both Poisson and negative binomial models) (Fig. 3). The number needed to treat to prevent one acute exacerbation of COPD was 2.86.

SECONDARY OUTCOMES

The effect of azithromycin on the secondary outcomes is summarized in Table 2. The effect of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage (which ranges from stage I COPD, indicating mild disease, to stage IV COPD, indicating very severe disease) on the rate of acute exacerbations of COPD and on frequency of hospitalizations is presented in Section B in the Supplementary Appendix, available at NEJM.org. The total SGRQ scores recorded at 1 year decreased a mean ($\pm$ SD) of 2.8 ± 12.8 units in the azithromycin group, as compared with a mean of 0.6 ± 11.4 units in the placebo group ($P=0.004$) (see Section C in the Supplementary Appendix for individual scale scores). Although this mean change did not exceed the minimal clinically important difference of at least 4 units, more participants in the azithromycin group than in the placebo group had a decrease of at least 4 units in their SGRQ score (43% vs. 36%, $P=0.03$). No consistent changes were seen in the scores on the SF-36 (see Section D in the Supplementary Appendix). The mean rate of adherence to the study medication was 67.3% in the azithromycin group and 66.9% in the placebo group ($P=0.84$).

SUBGROUP ANALYSES

Analyses were performed according to 22 subgroups; the results are provided in Section I in the Supplementary Appendix. The subgroup analyses showed that the response to azithromycin seemed to vary according to age (≤ 65 vs. >65 years), smoking status (former

smoker vs. current smoker), use or nonuse of oxygen, GOLD stage, and use or non-use of inhalers.

ADVERSE EVENTS

The rate of death from any cause was 3% in the azithromycin group and 4% in the placebo group ($P=0.87$). The rate of death from respiratory causes was 2% and 1% in the two groups, respectively ($P=0.48$), and the rate of death from cardiovascular causes was 0.2% in both groups ($P=1.00$) (see Section H in the Supplementary Appendix). No significant differences were observed in the frequency of serious adverse events or of adverse events leading to discontinuation of the study drug, but an audiogram-confirmed hearing decrement occurred in 142 of the participants receiving azithromycin (27%), as compared with 110 of those receiving placebo (21%) ($P=0.04$). A small but significant between-group difference was observed in the mean age-adjusted hearing thresholds for the four sound frequencies from enrollment to month 3, with patients in the azithromycin group having more pronounced hearing decrements (see Section F in the Supplementary Appendix). In 80 participants receiving azithromycin and in 45 receiving placebo, the hearing decrement occurred before the 12-month visit, providing the opportunity to determine whether hearing returned within a minimum of 1 month after discontinuation of the study drug. Although all of these participants should have had their study drug discontinued, the drug was discontinued in only 61 participants in the azithromycin group (76%) and 37 in the placebo group (82%), owing to protocol errors. Subsequent audiograms showed that hearing improved to the baseline level in 21 of the 61 participants (34%) who discontinued azithromycin and in 6 of the 19 (32%) who did not, as well as in 14 of the 37 participants (38%) who discontinued placebo and in 2 of the 8 (25%) who did not.

NASOPHARYNGEAL COLONIZATION AND RESISTANCE TO MACROLIDES

Nasopharyngeal swabs were obtained at 85% and 84% of the clinic visits attended by participants in the azithromycin group and placebo group, respectively. A total of 79 of the 558 participants who were randomly assigned to receive azithromycin and had at least one follow-up visit (14%) and 83 of the 559 participants who were randomly assigned to receive placebo and had at least one follow-up visit (15%) were colonized with selected respiratory pathogens at the time of enrollment ($P=0.81$). A total of 66 of the participants in the azithromycin group (12%) and 172 in the placebo group (31%) who had not had nasopharyngeal colonization at the time of enrollment became colonized during the course of the study ($P<0.001$). No association was seen between nasopharyngeal colonization either at the time of enrollment or any time thereafter and the occurrence of acute exacerbations of COPD ($P=0.31$).

Cultures from 56% of the participants in the azithromycin group and 59% in the placebo group who had selected respiratory pathogens cultured from their nasopharyngeal swabs at the time of enrollment were available for susceptibility testing ($P=0.68$); the remaining cultures were not tested because of protocol errors. The prevalence of resistance to macrolides was 52% and 57% in the two groups, respectively ($P=0.64$). Cultures from 68% of the participants in the azithromycin group and 70% in the placebo group who were not colonized with selected respiratory pathogens at the time of enrollment but who became colonized during the course of the study were available for susceptibility testing ($P=0.76$), and the incidence of resistance to macrolides was 81% and 41% in the two groups, respectively ($P<0.001$) (Section G in the Supplementary Appendix).

DISCUSSION

Among subjects at increased risk for acute exacerbations of COPD who received azithromycin, at a dose of 250 mg once daily, for 1 year in addition to their usual care, the frequency of acute exacerbations was decreased. This decrease was accompanied by a decrease in the incidence of colonization with selected respiratory pathogens and improved quality of life, but also an increase in the incidence of colonization with macrolide-resistant organisms and an excess rate of hearing decrements of approximately 5%.

Seven previous studies have evaluated whether macrolide antibiotics decrease the risk of acute exacerbations of COPD. Two of the studies showed no effect, but one of these used a retrospective design²⁹ and the other was conducted for only 3 months, and very few acute exacerbations of COPD occurred in either group.²⁶ Five studies have reported that macrolides decrease acute exacerbations of COPD, but one of these was not a blinded study,²⁷ two did not include concurrent controls,^{31,32} and one involved only 35 patients.³⁰ Seemungal and colleagues performed a well-designed, randomized, 1-year trial of erythromycin, at a dose of 250 mg twice daily, in 109 patients (a study that was stopped before the target enrollment was met).²⁸ The relative rate of acute exacerbations of COPD among the treated participants was 0.65. The median time to the first acute exacerbation among the participants who received erythromycin was 271 days, similar to the 266 days we found among the participants in our study who received azithromycin. However, Seemungal and colleagues found that in the control group the median time to the first acute exacerbation was 89 days, whereas in our study it was 174 days, perhaps because nearly 40% of the participants in their study had had three or more acute exacerbations in the year before enrollment, more were current smokers, and fewer were receiving long-acting muscarinic antagonists.

Since approximately 80% of our participants were taking inhaled glucocorticoids with or without long-acting beta₂-agonists or long-acting muscarinic antagonists throughout the study, the ability of azithromycin to decrease the frequency of acute exacerbations would seem to be additive to these other therapies.

None of the previous studies of the effect of macrolides on acute exacerbations of COPD either assessed or reported hearing problems as a complication.^{26–32} We found that more participants receiving azithromycin met the criteria for development of a hearing decrement than did those receiving placebo, but the improvements in hearing that occurred on repeat testing, regardless of whether the study drug was discontinued, suggest that our criteria were too stringent and that the incidence of hearing decrements was overestimated in both groups.

Participants receiving azithromycin were less likely to become colonized with respiratory pathogens but were more likely to become colonized with macrolide-resistant organisms (contrary to the findings of Seemungal and colleagues²⁸). Despite this, we found no evidence suggesting that colonization increased the incidence of acute exacerbations of COPD or pneumonia, consistent with prior observations in patients with cystic fibrosis.^{37,38} Although we saw no adverse cardiac effects of azithromycin, risk factors for the prolongation of the QTc interval were assessed before enrollment and participants who were thought to be at risk were excluded.

We chose a 250-mg dose of azithromycin because we thought that it was high enough to limit the possibility that a negative result might occur because of insufficient dosing. We administered the dose daily, rather than less frequently, to facilitate adherence. It is possible that lower doses or less frequent administration could have produced similar results.

Sputum samples are preferred for the assessment of bacterial colonization. When we began the study, we obtained both expectorated sputum samples and nasopharyngeal swabs because we knew that some patients would not be able to produce sputum. By the third month, however, less than 15% of participants had been able to produce sputum, causing us to restrict our subsequent assessments of colonization to an assessment of deep nasopharyngeal swabs. Patel and colleagues³⁹ found that 52% of patients with frequent acute exacerbations of COPD had induced sputum that was most commonly colonized with *Haemophilus influenzae*, *S. pneumoniae*, *H. parainfluenzae*, and *Moraxella catarrhalis*. Although we found a much lower rate of nasopharyngeal colonization than did Patel et al. (approximately 15% of patients at the time of enrollment), the most common pathogens were similar (with the exception that *S. aureus* was cultured more frequently in our study, as would be expected from nasopharyngeal sampling), and the effect of taking macrolides on colonization with macrolide-resistant respiratory pathogens was still clearly apparent.

We cannot comment on the safety profile of azithromycin when it is taken for longer than 1 year, and we have no information pertaining to potential effects of long-term macrolide administration on bacterial resistance patterns in the community. Our results should be applied only to patients with COPD who either require supplemental oxygen or have had acute exacerbations and who do not have resting tachycardia or prolongation of the QTc interval, are not taking medications associated with QTc prolongation, and do not have hearing abnormalities that place them below the 95th percentile of patients of similar age.

In summary, we found that adding azithromycin, at a dose of 250 mg daily, for 1 year to the usual treatment of patients who have an increased risk of acute exacerbations of COPD but no hearing impairment, resting tachycardia, or apparent risk of QTc prolongation decreased the frequency of acute exacerbations of COPD and the incidence of colonization with selected respiratory pathogens and improved quality of life but increased the incidence of colonization with macrolide-resistant organisms and decreased hearing in a small percentage of participants. Given the deleterious effects of acute exacerbations of COPD with respect to the risk of death, quality of life, loss of lung function, and cost of care, adding azithromycin to the treatment regimen of patients who have had an acute exacerbation of COPD within the previous year or who require supplemental oxygen is a valuable option; however, the patients should be screened for the presence of QTc prolongation and the risk of QTc prolongation and their hearing should be monitored. In addition, it should be recognized that the long-term effects of this treatment on microbial resistance in the community are not known.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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Patients who completed the 12-month course of the study drug were asked to return 1 month later for a washout visit. FEV₁ denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

Figure 2. Proportion of Participants Free from Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) for 1 Year, According to Study Group

The analyses were based on the participants who were randomly assigned to the group minus those who did not return for any follow-up assessment — 558 participants in the azithromycin group, of whom 317 (57%) had an acute exacerbation, and 559 in the placebo group, of whom 380 (68%) had an acute exacerbation.

Figure 3. Rates of Acute Exacerbations of Chronic Obstructive Pulmonary Disease per Person-Year, According to Study Group

Table 1

Baseline Clinical and Demographic Characteristics of the Patients. *

Characteristic	Azithromycin (N = 558)	Placebo (N = 559)
Age — yr	65±9	66±8
Female sex — no. (%)	229 (41)	227 (41)
Race or ethnic group — no. (%) [†]		
White	456 (82)	449 (80)
Black	75 (13)	86 (15)
Other	19 (3)	22 (4)
Multiethnic	19 (3)	16 (3)
Postbronchodilator FEV ₁		
Liters	1.10±0.50	1.12±0.52
% of predicted value	39±16	40±16
Ratio of FEV ₁ to FVC — %	42±13	43±13
GOLD stage — no. (%) [‡]		
II	144 (26)	148 (26)
III	225 (40)	226 (40)
IV	188 (34)	182 (33)
Smoking history — pack-yr	58±32	59±32
Current smoker — no. (%)	119 (21)	127 (23)
Medications for COPD — no. (%)		
Inhaled glucocorticoids only	21 (4)	36 (6)
LAMAs only	34 (6)	43 (8)
LABAs only	15 (3)	6 (1)
Inhaled glucocorticoids and LABAs	104 (19)	125 (22)
Inhaled glucocorticoids and LAMAs	23 (4)	28 (5)
LABAs and LAMAs	30 (5)	23 (4)
Inhaled glucocorticoids, LABAs, and LAMAs	273 (49)	255 (46)
None	58 (10)	43 (8)
Entry criteria		
Acute exacerbation of COPD in previous 12 mo requiring hospitalization or emergency room visit — no. (%)	278 (50)	283 (51)
Systemic glucocorticoids for acute exacerbation of COPD in previous 12 mo — no. (%)	467 (84)	477 (85)
Long-term oxygen — no. (%)	334 (60)	328 (59)
Long-term oxygen as the only criterion — no. (%)	72 (13)	65 (12)

* Plus-minus values are means ±SD. The total numbers in the two groups are the number of participants who were randomly assigned to the group (570 to the azithromycin group and 572 to the placebo group) minus those who did not return for any follow-up assessment (12 in the azithromycin group and the 13 in the placebo group). There were no significant between-group differences ($P>0.05$ for all comparisons). COPD denotes chronic obstructive pulmonary disease, FEV₁ forced expiratory volume in 1 second, FVC forced vital capacity, LABA long-acting beta₂ agonist, and LAMA long-acting muscarinic antagonist.

[†] Race or ethnic group was self-reported. Other groups included Native Americans, Asians, Hispanics, and Pacific Islanders. A breakdown according to these groups is provided in Section A in the Supplementary Appendix, available at NEJM.org.

[‡] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage ranges from stage I COPD, indicating mild disease, to stage IV COPD, indicating very severe disease.

Effect of Treatment for Chronic Obstructive Pulmonary Disease (COPD) on Hospitalization Rates, Emergency Department or Urgent Care Visits, and Unscheduled Office Visits.

Table 2

Event	Azithromycin		Placebo		P Value *	Hazard Ratio (95% CI) [†]		P Value [‡]
	no. of events	mean events/ patient-yr (95% CI)	no. of events	mean events/ patient-yr (95% CI)				
Hospitalization for any cause	323	0.74 (0.60–0.89)	329	0.95 (0.76–1.18)	0.13	0.94 (0.76–1.15)		0.52
Hospitalization related to COPD	156	0.34 (0.26–0.43)	200	0.49 (0.31–0.67)	0.14	0.82 (0.64–1.07)		0.15
Emergency department or urgent care visit	199	0.43 (0.34–0.53)	257	0.48 (0.39–0.57)	0.47	0.81 (0.63–1.04)		0.09
Unscheduled office visit	1202	2.46 (2.08–2.48)	1345	2.57 (2.21–2.60)	0.048	0.85 (0.74–0.98)		0.02
Intubations	11	0.02 (0.01–0.04)	16	0.04 (0.01–0.06)	0.23	0.79 (0.04–1.75)		0.56

*The P value is for the rate of events per patient-year.

[†]The hazard ratio and P value are for the time to the first event in the azithromycin group as compared with the placebo group.