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ORIGINAL ARTICLE

Predictors of Chronic Obstructive Pulmonary Disease Exacerbation Reduction in Response to Daily Azithromycin Therapy

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Abstract

Rationale: Daily azithromycin decreases acute exacerbations of chronic obstructive pulmonary disease (AECOPD), but long-term side effects are unknown.

Objectives: To identify the types of exacerbations most likely to be reduced and clinical subgroups most likely to benefit from azithromycin, 250 mg daily, added to usual care.

Methods: Enrollment criteria included irreversible airflow limitation and AECOPD requiring corticosteroids, emergency department visit, or hospitalization in the prior year or use of supplemental oxygen. Recurrent events and cumulative incidence analyses compared treatment received for AECOPD by randomization group, stratified by subgroups of interest. Cox proportional hazards models estimated treatment effects in subgroups adjusted for age, sex, smoking status, FEV_1% predicted, concomitant COPD medications, and oxygen use.

Measurements and Main Results: Azithromycin was most effective in reducing AECOPD requiring both antibiotic and steroid treatment (n = 1,113; cumulative incidence analysis, $P = 0.0002$; recurrent events analysis, $P = 0.002$). No difference in treatment response by sex ($P = 0.75$), presence of chronic bronchitis ($P = 0.19$), concomitant inhaled therapy ($P = 0.29$), or supplemental oxygen use ($P = 0.23$) was observed. Older age and milder Global Initiative for Chronic Obstructive Lung Disease stage were associated with better treatment response ($P = 0.02$ and 0.04, respectively). A significant interaction between treatment and current smoking was seen ($P = 0.03$) and azithromycin did not reduce exacerbations in current smokers (hazard ratio, 0.99; 95% confidence interval, 0.71–1.38; $P = 0.95$).

Conclusions: Azithromycin is most effective in preventing AECOPD requiring both antibiotic and steroid treatment. Adjusting for confounders, we saw no difference in efficacy by sex, history of chronic bronchitis, oxygen use, or concomitant COPD therapy. Greater efficacy was seen in older patients and milder Global Initiative for Chronic Obstructive Lung Disease stages. We found little evidence of treatment effect among current smokers. Clinical trial registered with www.clinicaltrials.gov (NCT0011986 and NCT00325897).

Keywords: chronic obstructive pulmonary disease; exacerbation; quality of life; azithromycin

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At a Glance Commentary

Scientific Knowledge on the Subject: Daily azithromycin decreases acute exacerbations of chronic obstructive pulmonary disease but the risk-benefit ratio must be maximized and it is not known which subjects benefit most from therapy.

What This Study Adds to the Field: This comprehensive analysis demonstrates that the treatment benefit of azithromycin is greatest in ex-smokers, older subjects, and milder Global Initiative for Chronic Obstructive Lung Disease stages, whereas sex, concomitant chronic obstructive pulmonary disease therapy, and presence of chronic bronchitis does not seem to influence the response. Azithromycin is particularly effective in reducing acute exacerbations of chronic obstructive pulmonary disease requiring both antibiotic and steroid treatment.

We recently reported that azithromycin, taken daily for 1 year, decreased acute exacerbations of chronic obstructive pulmonary disease (AECOPD), but was associated with a greater incidence of minor hearing loss and nasopharyngeal colonization with azithromycin-resistant organisms (1). Consequently, it is important to identify subjects most likely to respond to optimize the risk-benefit ratio. Our initial unadjusted analyses suggested that the efficacy of azithromycin in reducing AECOPD may differ as a function of age, smoking status, concomitant inhaled therapy, oxygen use, and Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage (1). However, these analyses were unadjusted for potential confounders. Also left unexplored was the type of exacerbations most influenced by azithromycin therapy: those requiring treatment with antibiotics, steroids, or both. Hence, using data from the National Institutes of Health–sponsored azithromycin in COPD trial, we sought to determine the treatment effect of azithromycin in specific patient subpopulations, the efficacy of azithromycin in the setting of various concomitant therapies, and the types of AECOPD most likely to be reduced while adjusting for potentially relevant confounders.

Methods

Subjects and Trial Design

The study design has been previously published (1). The population comprised 1,142 subjects with COPD who were randomized to usual treatment (i.e., any combination of inhaled treatments for COPD) plus either azithromycin (250 mg) or placebo taken daily for 12 months. Eligibility criteria included a clinical diagnosis of COPD and age greater than or equal to 40 years. To enrich the population with participants more likely to experience AECOPDs, subjects also had to either be using continuous supplemental oxygen or have had an AECOPD within the previous 12 months (defined as requiring systemic corticosteroids, an emergency room visit, or a hospitalization) (2). Subjects could not be enrolled within 4 weeks of an AECOPD.

Subjects were monitored for AECOPDs at clinic visits that occurred at 3-month intervals and by telephone contacts that occurred monthly between clinic visits. The St. George's Respiratory Questionnaire, a validated health status instrument in COPD (3), was administered at enrollment and used to define chronic bronchitis as cough either most days or several days a week and phlegm most days or several days a week during the last year. For purposes of this study, an AECOPD was defined as respiratory symptoms (increased or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with duration of at least 3 days requiring treatment with antibiotics or systemic steroids.

Statistical Analysis

All analyses were performed in R (www.r.org). Data were truncated at 380 days consistent with the primary analysis. The final dataset (n = 1,113) consisted of patients with complete data on the variables of interest (i.e., every confounder used in the Cox proportional hazards model as outlined next). Student *t* tests and chi-square tests were used to compare continuous and categorical characteristics, respectively. Cox proportional hazards regression models on the endpoint of time to first exacerbation were used to estimate treatment effect in the subgroups. Each model was stratified by clinical center and included age, sex, smoking status at baseline, FEV_1% predicted at baseline, concomitant inhaled medications for COPD, and oxygen use with the following exception: GOLD analyses were adjusted for GOLD spirometry classification rather than for FEV_1%. Exacerbation rates per year for subgroup analyses were based on a negative binomial model; this model is often used as an alternative to Poisson regression for rates when data are overdispersed, which was the case for our data (4). A proportional means model for the number of exacerbations by type (antibiotics alone, steroids alone, or both) was performed to assess differences between randomization groups (5). We also used a cumulative incidence function analysis to compare randomization groups by first exacerbation type, which accounts for the competing risk nature of exacerbation types (6).

Results

The analysis included 1,113 subjects (99.6% of the 1,117 subjects reported in the primary analysis) (*see* Figure E1 in the online supplement). One subject in the treatment arm was missing smoking status and three subjects in the placebo arm were missing baseline FEV_1 data. Age, sex, smoking history, and GOLD stage were similar across treatment groups (Table 1). A small difference in the distribution of concurrent therapies was seen between treatment groups ($P = 0.04$). Compared with placebo, a slightly greater percentage of azithromycin-treated subjects received a combination of inhaled corticosteroids (ICS), long-acting muscarinic agents (LAMA), and long-acting β-agonists (LABA), 49% versus 45%. Slightly more placebo-treated subjects received ICS-LABA combination therapy, 22% versus 19% (Table 1). Unadjusted exacerbation rates and risk for exacerbation by subgroup in the placebo-treated arm are reported in Table E1. Compared with males, females had a 1.26 times higher frequency of exacerbations (95% confidence interval [CI], 1.02–1.52; $P = 0.01$). Subjects with chronic bronchitis had a 1.24 times higher frequency of exacerbations than those without (95% CI, 1.04–1.49; $P = 0.02$).

Table 1. Subject Demographics

Characteristic	Placebo (*n = 556*)	Azithromycin (*n = 557*)	*P* Value
Age, yr (mean ± SD)	66 ± 9	65 ± 9	0.18
Female sex, n (%)	226 (41)	229 (41)	0.92*
Post-bronchodilator FEV_1			
Liters (mean ± SD)	1.12 ± 0.52	1.10 ± 0.50	0.47
% of predicted value	40 ± 16	39 ± 16	0.42
FEV_1/FVC, %	43 ± 13	42 ± 13	0.49
GOLD stage, n (%)			0.93*
II	148 (27)	144 (26)	
III	226 (41)	225 (40)	
IV	182 (33)	188 (34)	
Smoking history, pack-years (mean ± SD)	59 ± 32	58 ± 32	0.66
Current smoker, n (%)	127 (23)	119 (21)	0.60*
Medications for COPD, n (%)			0.04*
None	43 (8)	57 (10)	
ICS only	36 (6)	21 (4)	
LAMA only	43 (8)	34 (6)	
LABA only	6 (1)	15 (3)	
ICS and LABA	125 (22)	104 (19)	
ICS and LAMA	28 (5)	23 (4)	
LAMA and LABA	23 (4)	30 (5)	
ICS, LAMA, and LABA	252 (45)	273 (49)	
SGRQ symptoms score	61 ± 19	62 ± 20	0.31
SGRQ activity score	69 ± 20	70 ± 19	0.29
SGRQ impact score	36 ± 18	36 ± 19	0.62
SGRQ total score	50 ± 16	51 ± 16	0.38
Chronic bronchitis symptom, n (%)	251 (45)	275 (50)	0.19
Entry criteria			
Long-term oxygen, n (%)	325 (58)	334 (60)	0.65*

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β-agonists; LAMA = long-acting muscarinic agents; SGRQ = St. George's Respiratory Questionnaire.
**P* value from chi-square test. The rest of the *P* values are from a two-sample *t* test.

To determine if azithromycin influenced the type of treatment received for exacerbation events we used a proportional means model to compare the two randomization groups with respect to the number of exacerbations that required treatment with both antibiotics and steroids. We found that the azithromycin-treated group had 0.76 (95% CI, 0.63–0.91; $P = 0.002$) times fewer exacerbations requiring both antibiotics and steroids compared with placebo-treated subjects. In comparison, using this model, the azithromycin-treated group had 0.83 (95% CI, 0.72–0.95; $P = 0.009$) times fewer exacerbations requiring either antibiotics alone, steroids alone, or both as the placebo group. Hence, azithromycin seems to be particularly effective in preventing exacerbations requiring more intense pharmacotherapy. An additional cumulative incidence analysis also supports this finding. In this complementary analysis, we examine the time to first exacerbation in azithromycin versus placebo patients comparing antibiotic-treated events, steroid-treated events, and antibiotic- and steroid-treated events accounting for the fact that occurrence of one type of first event precludes the occurrence of the other two. Figure 1 shows cumulative incidence functions for first exacerbation by treatment modality (antibiotics alone, steroids alone, or both). Again, in examining first exacerbations receiving antibiotics alone (n = 214), steroids alone (n = 110), or both (n = 377), we observed the treatment effect on cumulative incidence of first exacerbations treated with both antibiotics and steroids in azithromycin-treated subjects as compared with placebo ($P = 0.0002$).

We next conducted subgroup analyses for time to first exacerbation according to categorical variables (Table 2). The hazard ratio (HR) in ex-smokers and current smokers was 0.65 (95% CI, 0.55–0.77; $P < 0.0001$) and 0.99 (95% CI, 0.71–1.38; $P = 0.95$). The *P* value for interaction between smoking status and treatment was 0.03, suggesting a significant difference in treatment benefit by smoking status with those not actively smoking receiving more benefit. In subjects with symptoms of chronic bronchitis, the HR for exacerbation reduction with azithromycin was 0.76 (95% CI, 0.62–0.94; $P = 0.01$) versus 0.64 (95% CI, 0.52–0.80; $P = 0.0001$) for those without. However, the interaction between chronic bronchitis and treatment indicated no significant difference in treatment effect between groups ($P = 0.25$).

Inhaled treatment regimens encompassed by "usual care" included all combinations of ICS, LAMAs, and LABAs. The *P* value for interaction between concurrent medications and treatment effect was not significant ($P = 0.29$) indicating no strong evidence for difference in the response by concurrent COPD medication included. The HRs for exacerbation reduction in subjects who did and did not require supplemental oxygen was 0.80 (95% CI, 0.62–1.03; $P = 0.08$) and 0.66 (95% CI, 0.55–0.80; $P < 0.0001$), respectively, but the interaction did not achieve statistical significance ($P = 0.23$) suggesting against treatment effect modification by concomitant oxygen use. No evidence for a difference in treatment effect was observed for women versus men ($P = 0.75$) with a HR for exacerbation reduction being 0.69 for women (95% CI, 0.55–0.87; $P = 0.001$) and 0.72 for men (95% CI, 0.59–0.89; $P = 0.002$). However, an increased treatment response for milder GOLD stages was observed ($P = 0.04$, linear trend test). HRs by GOLD stage were 0.57 (95% CI, 0.43–0.74; $P < 0.001$), 0.69 (95% CI, 0.59–0.81; $P < 0.001$), and 0.85 (95% CI, 0.67–1.07; $P = 0.16$) for GOLD stages II (n = 292), III (n = 451), and IV (n = 370), respectively. For continuous variables, we chose graphical display for easier interpretation. A significant interaction between age and treatment effect on risk for AECOPD was detected ($P = 0.02$). From Figure 2 it can be seen that treatment benefit increases with age.

The initially published, unadjusted findings raised concerns for less efficacy of azithromycin among smokers, younger individuals, higher GOLD stages, those treated with ICS, and individuals not on oxygen therapy (1). In the present analyses that are adjusted for potential confounders, we did not find strong evidence that inhaled

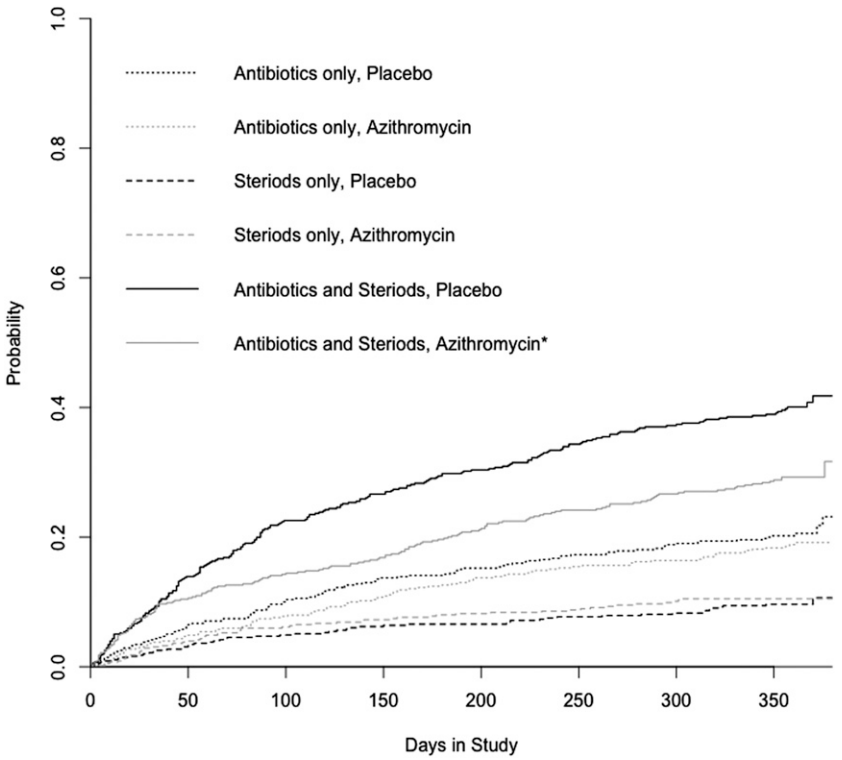

Figure 1. Plot demonstrating the differences in cumulative incidence of first exacerbations stratified by randomization group and exacerbation type as classified by treatment with antibiotics only, steroids only, or both. This demonstrates that azithromycin's effectiveness is most evident in preventing exacerbations requiring antibiotics and steroids. *Comparing cumulative incidence in patients who received antibiotics and steroids for their exacerbation between randomization groups, $P = 0.0002$. Comparisons by randomization group for other exacerbation types were not statistically significant (steroids only, $P = 0.68$; antibiotics only, 0.41).

concomitant therapies or oxygen usage significantly influenced treatment response but our data do support less efficacy of azithromycin among current smokers, younger individuals, and higher GOLD stages. Hence, to further understand the influence of azithromycin among subgroups where our data support less treatment effect, we also performed cumulative incidence analyses for first exacerbation by treatment modality (antibiotics alone, steroids alone, or both) additionally stratified by these smoking status, age, and GOLD stage. In Figure E2 where the analysis is restricted to smokers, we see no significant difference between azithromycin- and placebo-treated subjects for any of the exacerbation subgroups (antibiotics and steroids, $P = 0.83$; antibiotics, $P = 0.21$; steroids $P = 0.21$). In Figure E3 the analysis is restricted to individuals age less than or equal to 65. There is a trend for greatest treatment effect on exacerbations requiring treatment with antibiotics and steroids ($P = 0.19$) and less for exacerbations requiring antibiotics alone ($P = 0.87$) or steroids alone ($P = 0.77$). In Figure E4, the analysis is restricted to GOLD IV individuals. Here we see the most pronounced separation between the azithromycin- and placebo-treated subjects for more severe exacerbations requiring treatment with antibiotics and steroids, $P = 0.04$ with less effect for exacerbations requiring antibiotics alone ($P = 0.86$) or steroids alone ($P = 0.38$).

Discussion

These additional analyses were performed to aid the understanding of the types of exacerbations and patients with COPD for which chronic azithromycin therapy might be more effective. We demonstrated azithromycin's effect is most pronounced in preventing AECOPD treated with both antibiotics and steroids. In the adjusted, multivariate subgroup analyses, we found no strong evidence to support a difference in chronic azithromycin therapy efficacy based on sex, history of chronic bronchitis, oxygen use, or concomitant COPD therapy. Although we did demonstrate azithromycin may be more effective in older subjects and milder GOLD stages, our analyses still suggest AECOPD reductions are seen in younger patients and higher GOLD stages, particularly exacerbations requiring treatment with antibiotics and steroids. We found little evidence to support the efficacy of azithromycin in current smokers.

An intriguing finding of our analyses is that the effects of azithromycin seem to be most pronounced in preventing exacerbations requiring the most intense pharmacotherapy. This suggests azithromycin may be effective in preventing more severe exacerbations. In our original analyses, we saw fewer hospitalizations for COPD in azithromycin-treated subjects (0.34 events per patient-year) as compared with placebo (0.49 events per patient-year); however, these analyses were underpowered and did not achieve statistical significance ($P = 0.15$) (1). Although there were 156 hospitalizations for COPD events in the azithromycin-treated group and 200 in the placebo group, we noted a total of 379 exacerbation events requiring antibiotics and steroids in the azithromycin-treatment group versus 501 in the placebo group.

A strength of the parent protocol included that all concomitant COPD therapies were allowed including LAMAs, LABAs, and LABA-ICS combination. Importantly, we observed no significant interaction between these treatments and azithromycin suggesting against a modification in azithromycin's efficacy by common concomitant COPD therapies. Although some treatment regimens contained few patients, azithromycin demonstrated effectiveness in subjects already being treated with LAMA, LABA, and ICS suggesting that azithromycin provides additional benefit to patients treated with "maximal" inhaled therapies.

We demonstrate that azithromycin seems to be more effective in older individuals, but there is a wide 95% CI at lower ages and we caution against interpretation that azithromycin is ineffective in younger individuals. Our cumulative incidence analysis suggests a trend toward the greatest impact of azithromycin in individuals less than or

Table 2. Hazard Ratio (Azithromycin/Placebo) for Time to First Exacerbation in Subgroup

Subgroup (n)	HR	95% CI for HR	*P* Value*	*P* Value for Interaction
All (1,113)	0.71	0.61–0.83	<0.0001	
Women (455)	0.69	0·55–0.87	0.001	0.75
Men (658)	0.72	0.59–0.89	0.002	
GOLD II (292)	0.55	0.40–0.75	0.0002	0.04
GOLD III (451)	0.71	0.56–0.90	0.004	
GOLD IV (370)	0.84	0.65–1.08	0.18	
Ex-smoker (867)	0.65	0.55–0.77	<0.0001	0.03
Smoker (246)	0.99	0.71–1.38	0.95	
Chronic bronchitis symptoms present (526)	0.76	0.62–0.94	0.01	0.25
Chronic bronchitis symptoms absent (581)	0.64	0.52–0.80	0.0001	
No ICS, LAMA, LABA (100)	0.42	0.23–0.77	0.005	0.29
ICS only (57)	0.65	0.31–1.38	0.26	
LAMA only (77)	0.60	0.33–1.11	0.10	
LABA only (21)	0.42	0.15–1.18	0.10	
ICS and LAMA (51)	1.19	0.63–2.23	0.59	
ICS and LABA (229)	0.74	0.52–1.05	0.09	
LAMA and LABA (53)	0.47	0.23–0.98	0.04	
ICS, LAMA, and LABA (525)	0.76	0.62–0.94	0.01	
No long-term oxygen use (454)	0.80	0.62–1.03	0.08	0.23
Long-term oxygen use (659)	0.66	0.55–0.80	<0.0001	
Age ⩽ 65 (571)	0.84	0.68–1.04	0.1101	0.02
Age > 65 (542)	0.59	0.47–0.74	<0.0001	

Definition of abbreviations: CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; ICS = inhaled corticosteroids; LABA = long-acting β-agonists; LAMA = long-acting muscarinic agents.
All models included age, sex, clinic, smoking status at baseline, FEV_1% predicted at baseline, concomitant medications for COPD, and oxygen use except GOLD status models that used GOLD category instead of FEV_1%.

equal to 65 being on exacerbations requiring antibiotics and steroids in individuals. It should be noted that no significant difference in AECOPD frequency by age category in placebo-treated subjects was detected (*see* Table E1). It should also be noted that individuals with prolonged QTc and those taking medications known to prolong QTc were excluded from randomization. Because cardiac disease increases with age, although this patient population clearly benefits from azithromycin, appropriate screening of this patient population is also required.

We also detected a significant interaction between azithromycin treatment and lung function stratified by GOLD stage, which suggested a trend toward greater effect in patients with milder disease. However, we caution against concluding from these data that azithromycin is not effective in GOLD IV individuals. Our cumulative incidence analysis did find a significant effect of azithromycin on exacerbations requiring treatment with antibiotics and steroids in GOLD IV subjects.

We find little evidence, however, to support efficacy of azithromycin in current smokers. The mechanisms behind potential differences in efficacy we see in current smokers are incompletely understood. Azithromycin has been demonstrated to regulate MUC5AC expression and mucin production, likely at the transcriptional level (7). Smoking is associated with goblet cell hypersecretion and MUC5AC up-regulation (8). Hence, smoking could be counteracting effects of azithromycin on mucin production. Because smoking also impairs host innate immunity including ciliary clearance and macrophage, neutrophil, and lymphocyte function (9), azithromycin's antimicrobial effects may also contribute to these findings.

To place this work in the context of prior data, our larger study allowed multivariate analyses to examine patient subgroups. Only two other studies have examined azithromycin in COPD, one in 22 patients in an open-label randomized controlled trial (10) and the other 20 patients where clinical course was examined before and after treatment (11). Hence, our report is the first to be able to comment on the characteristics of patients most likely to respond to macrolide therapy.

We acknowledge several limitations to this analysis. First, this is a retrospective analysis of a study that was not specifically powered for subgroup analyses. Accordingly, not finding significant interactions between any of the confounders we examined and the treatment effect of azithromycin may be the result of type II errors. Because this manuscript addresses subgroup comparisons beyond the initially planned primary analysis, the possibility of

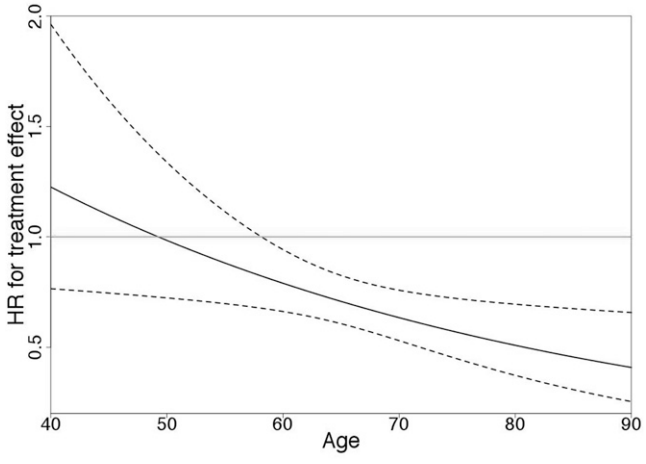

Figure 2. Hazard ratio (HR) for treatment effect for time to first exacerbation by age (*solid line*) with 95% point-wise confidence interval (*dashed lines*) (P = 0.02). Model stratified by clinical center and adjusted for sex, smoking status at baseline, FEV_1% predicted at baseline, concomitant medications for chronic obstructive pulmonary disease, and oxygen use.

spurious significant associations caused by multiple statistical tests is also a possibility. Second, the definition of chronic bronchitis that we used differed from the Medical Research Council definition of cough and sputum production for most days of 3 months a year for at least 2 years (12). Accordingly, our definition may not be sufficiently sensitive or specific to identify subjects who have an airway disease–predominant COPD phenotype, thereby diminishing our ability to detect a difference in treatment effect in subjects with chronic bronchitis. Finally, although this study was performed with daily azithromycin dosing, it is currently unknown whether daily versus three times weekly dosing in COPD optimizes the risk-benefit ratio. A clinical trial of three times weekly dosing in COPD is currently being conducted but the results are not yet available (13). Daily dosing was chosen because it was believed to minimize concerns that three times weekly dosing would not be enough to achieve clinical effect in this population, lack of published literature indicating side effect profile is increased with daily dosing, and at the urging of the NHLBI protocol review committee.

Finally, in weighing benefits and risks of azithromycin therapy, although not the focus of this analysis, consideration must also be made for potential side effects. We originally reported no significant difference in frequency of serious adverse events or of adverse events leading to drug discontinuation, but an audiogram-confirmed hearing decrement occurred in 25% of those receiving azithromycin versus 20% of those receiving placebo ($P = 0.04$) (1). In addition, a subset of participants had nasal culture data available for analysis demonstrating resistance to macrolides in 81% of azithromycin-treated patients and 41% of placebo-treated patients ($P < 0.001$) after treatment as compared with 52% and 57%, respectively, at baseline ($P = 0.64$). Although no association between colonization status and AECOPD was seen, patients were only treated for 1 year and long-term consequences of macrolide resistance on an individual level are unknown. Consideration must also be made for the risk of macrolide resistance at the population level, which has clearly increased coincident with the timing of azithromycin introduction (14).

In conclusion, this analysis demonstrates azithromycin's efficacy is most pronounced in reducing exacerbations requiring treatment with antibiotics and steroids as opposed to either alone such that azithromycin may also be a particularly promising therapy for patients who frequently experience these types of exacerbations. Although prospective data in predefined subgroups are still needed, these data also suggest that when adjusted for relevant confounders, azithromycin seems to be effective in reducing AECOPDs in both men and women, subjects with and without chronic bronchitis, oxygen use, or concomitant therapy. Greater efficacy was seen in older patients and milder GOLD stages. These data do suggest that azithromycin may be less effective in current smokers, hence treatment with azithromycin should be considered cautiously in this subgroup. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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