Azithromycin in Patients With Cystic Fibrosis Chronically Infected With *Pseudomonas aeruginosa*

A Randomized Controlled Trial

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Context Treatment strategies for cystic fibrosis (CF) lung disease include antibiotics, mucolytics, and anti-inflammatory therapies. Increasing evidence suggests that macrolide antibiotics might be beneficial in patients with CF.

Objective To determine if an association between azithromycin use and pulmonary function exists in patients with CF.

Design and Setting A multicenter, randomized, double-blind, placebo-controlled trial conducted from December 15, 2000, to May 2, 2002, at 23 CF care centers in the United States.

Participants Of the 251 screened participants with a diagnosis of CF, 185 (74%) were randomized. Eligibility criteria included age 6 years or older, infection with *Pseudomonas aeruginosa* for 1 or more years, and a forced expiratory volume in 1 second (FEV_1) of 30% or more. Participants were stratified by FEV_1 (≥60% predicted vs <60% predicted), weight of less than 40 kg vs 40 kg or more, and CF center.

Intervention The active group (n=87) received 250 mg (weight <40 kg) or 500 mg (weight ≥40 kg) of oral azithromycin 3 days a week for 168 days; placebo group (n=98) received identically packaged tablets.

Main Outcome Measures Change in FEV_1 from day 0 to completion of therapy at day 168 and determination of safety. Secondary outcomes included pulmonary exacerbations and weight gain.

Results The azithromycin group had a mean 0.097-L (SD, 0.26) increase in FEV_1 at day 168 compared with 0.003 L (SD, 0.23) in the placebo group (mean difference, 0.094 L; 95% confidence interval [CI], 0.023-0.165; $P=.009$). Nausea occurred in 17% more participatns in the azithromycin group ($P=.01$), diarrhea in 15% more ($P=.009$), and wheezing in 13% more ($P=.007$). Participants in the azithromycin group had less risk of experiencing an exacerbation than participants in the placebo group (hazard ratio, 0.65; 95% CI, 0.44-0.95; $P=.03$) and weighed at the end of the study an average 0.7 kg more than participants receiving placebo (95% CI, 0.1-1.4 kg; $P=.02$).

Conclusion Azithromycin treatment was associated with improvement in clinically relevant end points and should be considered for patients with CF who are 6 years or older and chronically infected with *P aeruginosa*.

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Cystic fibrosis (CF) is characterized by a recurrent cycle of pulmonary infection and inflammation. *Pseudomonas aeruginosa* is the most common pathogen in patients with CF and by age 18 years, 80% of patients are chronically infected. Neutrophils are the dominant inflammatory cells and much of the airway destruction characteristic of CF is secondary to neutrophil-derived proteases and oxidants.[1] Treatment strategies for CF lung disease have included antibiotics, mucolytics, and anti-inflammatory therapies.[2]

There is evidence suggesting that macrolide antibiotics may be beneficial for patients with CF. Macrolide antibiotics substantially reduced morbidity and mortality in patients in Japan with diffuse panbronchiolitis.[3,4] Diffuse panbronchiolitis shares many clinical features with CF; patients are often infected with mucoid strains of *P aeruginosa* and mortality is secondary to chronic pro-

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gressive lung disease. During the late 1990s, 2 small open-label studies suggested that macrolide antibiotics, particularly azithromycin, may benefit patients with CF.[5,6] In 2002, 2 small trials also reported benefit.[7,8] The mechanism of action of macrolide antibiotics is not known, but in vitro studies suggest that macrolide agents may decrease the production of bacterial virulence factors,[9,10] modulate the host inflammatory response, or both.[11]

We conducted a randomized, double-blind, placebo-controlled, multicenter trial in patients with CF chronically infected with *P aeruginosa* to determine if azithromycin administered for 24 weeks was safe, improved lung function, and decreased pulmonary exacerbations.

METHODS

Study Centers and Participant Selection Criteria

The trial was conducted at 23 CF Foundation accredited care centers in the United States between December 15, 2000, and May 2, 2002, and was coordinated by the CF Therapeutics Development Network Coordinating Center in Seattle, Wash. The institutional review board at each center approved the study and each participant or their parent/guardian voluntarily consented to participate. Eligibility criteria included a documented diagnosis of CF; age 6 years or older; weight of 25 kg or more; chronic infection with *P aeruginosa,* defined by a positive respiratory tract culture 1 year or more before screening and at screening; and a forced expiratory volume in 1 second (FEV_1) of 30% or more of predicted.[12] Exclusion criteria were *Burkholderia cepacia* complex isolated from the respiratory tract at screening or within 2 years of screening; nontuberculous mycobacteria within 2 years of screening or acid-fast bacillus smear positive at screening; history of biliary cirrhosis or portal hypertension, splenomegaly on examination, or liver function results (ie, aspartate serum transferase, alanine transferase, γ-glutamyltransferase phosphate) of 2 or more times the upper limit of normal; use of intravenous antibiotics, quinolones, or other oral antibiotics within 14 days of screening; use of systemic corticosteroids (≥20 mg of prednisone daily) within 30 days of screening; or initiation of tobramycin solution for inhalation,[13] recombinant human dornase alfa inhalation solution,[13,14] or high-dose ibuprofen[15] within 60 days of screening. Long-term use of these medications was permissible.

Randomization and Blinding

Approximately equal allocation to azithromycin and placebo groups was planned to achieve reasonable balance within categories of disease severity (≥60% or <60% of the predicted value of FEV_1) and weight (≥40 kg or <40 kg) and within each study site. Because of the large number of sites and the relatively small number of participants at each site, an allocation strategy used an algorithm that recalculated the proportion of participants at each site with each set of baseline clinical characteristics, before each randomization assignment.[16] Randomization assignments and a series of blinded drug kit numbers were generated by the CF Therapeutics Development Network Coordinating Center. Kits were distributed to the centers and a centralized secure randomization system at the coordinating center was used to assign drug kit numbers to patient identification numbers at each site. All study personnel and participants were blinded to treatment assignment. The randomization codes for each participant were revealed to the researchers once recruitment, data collection, and data analyses were completed.

Treatment Regimen

Azithromycin was supplied as 250-mg tablets and the placebo was identically packaged. Participants who weighed less than 40 kg were instructed to take 1 tablet 3 days a week (Monday, Wednesday, and Friday) and participants who weighed 40 kg or more were instructed to take 2 tablets on the same 3 days per week. The study drug was discontinued if a participant had an allergic reaction; a life-threatening adverse event, not including hospitalization for a pulmonary exacerbation; an adverse event that was considered intolerable by the site's study team or research participant; or if nontuberculous mycobacteria grew from a sputum sample obtained at screening. For participants with toxicity thought to be related to study drug (eg, gastrointestinal adverse effects), the study protocol included provisions for a step-down in the dosing regimen. Day-to-day care of the patient was left to the discretion of the CF care teams.

Clinical Evaluations

Medical history, physical examination, spirometry, oximetry, and chest radiograph were obtained at the screening visit (day –14). Clinical evaluations and spirometry were performed at days 0 (randomization), 28, 84, 168 (end of active treatment phase), and 196. Adverse events and concomitant medications were recorded during each visit and by telephone calls conducted on days 56, 112, and 140. Sputum samples or throat swabs were obtained at screening and on day 168. Additional sputum was collected from participants at 12 centers on days 28 and 168 to measure azithromycin concentrations.[17]

Blood samples to monitor hematology, liver function, and creatinine were obtained at screening, day 28, and day 168. The Cystic Fibrosis Quality of Life Questionnaire was administered to all English-speaking participants and parents/guardians on days 0 and 168.[18-20] Audiology testing was performed on participants at 11 centers on days 0 and 168. Hearing loss was defined as at least 10 dB increase in auditory threshold at 1 or more of the following frequencies: 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz.

Primary and Secondary Outcomes

The primary outcomes of the study were to determine if azithromycin was associated with a change in FEV_1 from day 0 to completion of therapy (day 168) and whether it was safe, as determined by adverse events including self-reported symptoms, physical findings, laboratory tests, audiology, and microbiology. Secondary outcomes in-

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cluded change in forced vital capacity (FVC), change in body weight, time until first pulmonary exacerbation, number of pulmonary exacerbations, hospitalization rates, use of nonquinolone oral antibiotics, changes in inflammatory markers, and quality of life. Exacerbations were defined as the use of intravenous antipseudomonal antibiotics or oral quinolones for 7 or more days.

Pulmonary function testing was performed in accordance with American Thoracic Society standards.[21] The FEV_1 and FVC measurements were expressed in liters and referenced to a healthy population as a percentage of predicted by using a modification of the Knudson equations.[12]

A standard microbiologic evaluation of sputum and throat cultures for potential pathogens was performed by the Therapeutics Development Network Microbiology Core Laboratory.[22] Acid fast bacillus smear and culture for nontuberculous mycobacteria were performed on sputum specimens only.[23]

Levels of IL-8 and neutrophil elastase activity were determined by the Therapeutics Development Network Inflammatory Markers Core Laboratory by using an enzyme immunoassay (R&D Systems, Minneapolis, Minn) and a kinetic spectrophotometric assay (Sigma Chemicals, St Louis, Mo), respectively.[24]

Sample Size Considerations

We hypothesized that the mean (SD) decrease in FEV_1 in the placebo group would be 0.05 (0.25) L and the mean (SD) increase in the azithromycin group would be 0.11 (0.28) L after 168 days of treatment. With these assumptions, a sample size of 88 participants per treatment group provided 97.5% power to detect a significant difference between treatment groups (2-sided $P = .05$). Participants were screened until a maximum of 185 participants were eligible for participation to account for attrition.

Statistical Methods

Analyses were conducted by the CF Therapeutics Development Network Coordinating Center according to a prespecified analysis plan and performed with a modified intent-to-treat principle that included all randomized participants who had at least 1 postbaseline measurement for the primary outcome. For the primary efficacy analysis, it was assumed a priori based on the results of other successful therapies for CF[13,14] that after an initial response to study drug, the FEV_1 of each participant would follow a linear pattern of decline, incline, or stabilization for the remainder of the treatment period. Given this assumption and to improve efficiency in the estimation of each participant's 168-day change from baseline, a derived variable approach[25] was used to estimate the change from baseline to day 168 for each participant. This approach maximizes the use of repeated FEV_1 measurements obtained throughout the study from each participant. For each participant, a piecewise linear regression vs time (actual days of day 0, 28, 84, and 168 visits) was fit to his/her FEV_1 data by using day 28 as the change point at which a maximum initial response would be observed. This regression model was used to estimate the 168-day change for each participant. The mean 168-day change across participants using these derived estimates was then compared between treatment groups by using a .05 level 2-sided *t* test. If a participant had insufficient data to compute the change using this approach (eg, were lost to follow-up), his/her day 0 FEV_1 measurement was subtracted from the last available measurement to estimate the change from baseline included in the primary analysis. The relative change in FEV_1% predicted, calculated as

$$\{[(FEV_1\%\ \text{predicted at day 168} - FEV_1\%\ \text{predicted at day 0}) \times 100]/FEV_1\%\ \text{predicted at day 0}\},$$

was also compared between treatment groups by using a .05 level 2-sided *t* test. Between-group comparisons of proportions were performed by using χ^2 test or the Fisher exact test, as appropriate. Mean changes between treatment groups in continuous outcome measures were compared with a 2-sample *t* test. Differences between groups in the linear rate of change from baseline in weight were estimated and tested using repeated measures regression with robust variance estimation.[26] Time to first exacerbation was assessed by using Cox proportional hazards regression model and graphically displayed using Kaplan-Meier method estimates. S-PLUS version 6.1 (Insightful Corp, Seattle, Wash) and SAS version 8.0 (SAS Institute, Cary, NC) were used for all statistical analyses. $P < .05$ was considered statistically significant.

RESULTS

Research Participants

Of the 251 participants screened for this study, 185 (74%) were randomized: 87 to the azithromycin group and 98 to the placebo group (FIGURE 1). Four participants in the azithromycin group and 6 in the placebo group were lost to follow-up. All but 1 participant in the placebo group, who was lost to follow-up before the day 28 visit, were included in the efficacy analysis. The median number of participants randomized per site was 8 (range, 3-17) at each of the 23 study sites. The baseline characteristics and randomization strata were similar between treatment groups (TABLE 1). Comparable proportions of participants in each group used long-term concomitant medications at baseline; recombinant human dornase alfa inhalation solution and tobramycin solution for inhalation were used by 75% and 61% of participants in the azithromycin group and 67% and 57% of participants in the placebo group, respectively. Compliance was monitored by the number of pills dispensed and returned, and was similar in both groups. On average, 93% of the weekly dosages in the azithromycin group and 89% of the weekly dosages in the placebo group were used.

Pulmonary Function

Participants in the azithromycin group had an estimated 0.097-L (SD, 0.26) improvement in FEV_1 at day 168 while participants in the placebo group had an estimated 0.003-L (SD, 0.23) improvement (mean difference, 0.094 L; 95% confidence interval [CI], 0.023-0.165;

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Figure 1. Flow Diagram of Participants

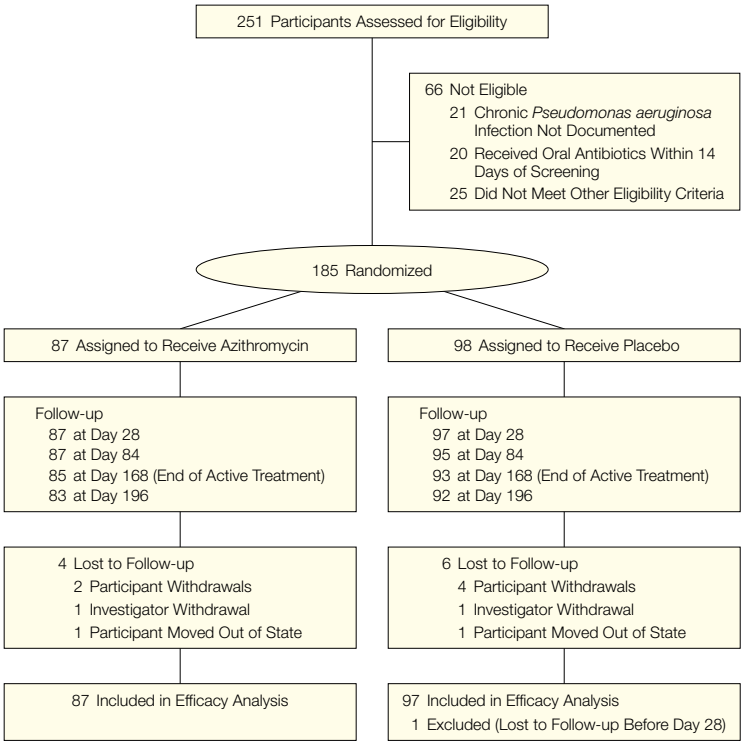

Table 1. Baseline Characteristics of the Participants According to Treatment Assignment*

Characteristics	Azithromycin (n = 87)	Placebo (n = 98)
Age, y		
6-12	9 (10.3)	10 (10.2)
13-17	35 (40.2)	40 (40.8)
≥18	43 (49.4)	48 (49.0)
Age, mean (SD), y	20.2 (7.9)	20.6 (8.6)
Female	42 (48.3)	46 (46.9)
% Predicted FEV_1		
≥60%	51 (58.6)	64 (65.3)
Mean (SD)	68.3 (21.2)	70.6 (23.7)
% Predicted FVC, mean (SD)	83.2 (18.4)	83.8 (20.0)
Weight, kg		
≥40	72 (82.8)	79 (80.6)
Mean (SD)	54.1 (14.4)	52.7 (14.0)
CF genotype		
ΔF_{508} homozygous	39 (44.8)	35 (35.7)
ΔF_{508} heterozygous	32 (36.8)	24 (24.5)
Other (non ΔF_{508})	3 (3.4)	3 (3.1)
Unknown	13 (15.0)	36 (36.7)

Abbreviations: CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
*Data are presented as No. (%) unless otherwise specified.

P=.009). As measured by the mean (SD) relative change from baseline in FEV_1% predicted, the azithromycin treatment group had a 4.4% (13.6%) improvement and the placebo group had a 1.8% (10.7%) decline (mean difference, 6.2%; 95% CI, 2.6%-9.8%; *P*=.001). The improvement in FEV_1 was noted at day 28 and sustained until day 168 but by day 196 (4 weeks after the active treatment was discontinued), FEV_1 returned to near baseline (FIGURE 2).

An improvement in FVC paralleled that observed for FEV_1. The mean (SD) improvement in FVC at day 168 was 0.14 (0.32) L in the azithromycin group and 0.02 (0.26) L in the placebo group (mean difference, 0.12 L; 95% CI, 0.04-0.20; *P*=.01). This corresponded with a 5.0% treatment effect in the relative change in FVC% predicted as the azithromycin group improved by 3.7% (SD, 11.8%) and the placebo group declined by 1.3% (SD, 9.0%) (mean difference, 5.0%; 95% CI, 1.9%-8.0%; *P*=.002).

Safety

Among the adverse events reported, only nausea, diarrhea, and wheezing were found to statistically differ between participants receiving azithromycin and those receiving placebo (TABLE 2). Nausea occurred in 17% more participants in the azithromycin group (95% CI, 5%-29%; *P*=.01), diarrhea in 15% more (95% CI, 4%-25%; *P*=.009), and wheezing in 13% more (95% CI, 4%-23%; *P*=.007). The majority of adverse events were described as mild or moderate in intensity. There were no statistically significant differences in laboratory abnormalities between azithromycin and placebo groups.

Two participants reported hearing impairment (1 in azithromycin group and 1 in placebo group), and 2 other participants reported tinnitus (1 in azithromycin group and 1 in placebo group). As judged by audiology testing, there was no evidence to suggest that hearing loss was more frequent in the azithromycin group (8 [18%] of 44) than in the placebo group (12 [24%] of 50; risk ratio, 0.8; 95% CI, 0.3-1.7).

The original dosage was either modified, or stopped and restarted in 8 participants (4 in each group). The majority of serious adverse events were related to hospitalization for pulmonary exacerbations. Study drug was discontinued in 3 participants in the azithromycin group and 2 in the placebo group. In the azithromycin group, study drug was discontinued because of sore feet and bruising (n=1), sinusitis (n=1), or rash and ankle pain (n=1).

Microbiology

The microbiologic profiles of the participants in each treatment group were similar at screening (TABLE 3). At day 168, 10% fewer participants in the azithromycin group had newly detected methicillin-susceptible *Staphylococcus aureus* (95% CI, –19% to –3%; *P*=.01). However, *S aureus* was not more likely to be eradicated in the azithromycin group; *S aureus* was eradicated from 18% of participants in the azithromycin group and 12% of participants in the placebo group (95% CI, –16% to 5%; *P*=.46). There was little difference between the 2 groups in the emergence or eradication of multidrug-resistant strains of *P aeruginosa* or other potential pathogens, including nontu-

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berculous mycobacteria. *P aeruginosa* density decreased by 0.3 log colony forming units at day 168 in the azithromycin group and increased by 0.2 log colony forming units in the placebo group (mean difference, 0.5 log colony forming units; 95% CI, 0.4-0.6; $P=.06$).

Weight Gain

The rate of weight change was found to be higher among participants in the azithromycin group than in the placebo group . Participants in the azithromycin group gained an average 0.7 kg more than participants in the placebo group by day 168 (95% CI, 0.1-1.4 kg; $P=.02$).

Hospitalizations and Antibiotic Use

Participants in the azithromycin group had less risk of experiencing an exacerbation than participants in the placebo group (hazard ratio, 0.65; 95% CI, 0.44-0.95; $P=.03$) (FIGURE 3). There was a reduction in the number of participants hospitalized and the mean number of days of nonquinolone oral antibiotic use in the azithromycin group (TABLE 4). Although not statistically significant, the azithromycin group experienced a 47% reduction in hospital days and a 39% reduction in the days of intravenous antibiotic use.

Quality of Life

Participants in the azithromycin group reported improvements in physical functioning on the CF Quality of Life Questionnaire in contrast with those in the placebo group (mean difference, 2.7; 95% CI, 0.1-5.3; $P=.05$). No significant differences were found between the groups in the scores for psychosocial functioning, body image factors, or total CF Quality of Life Questionnaire (TABLE 5).

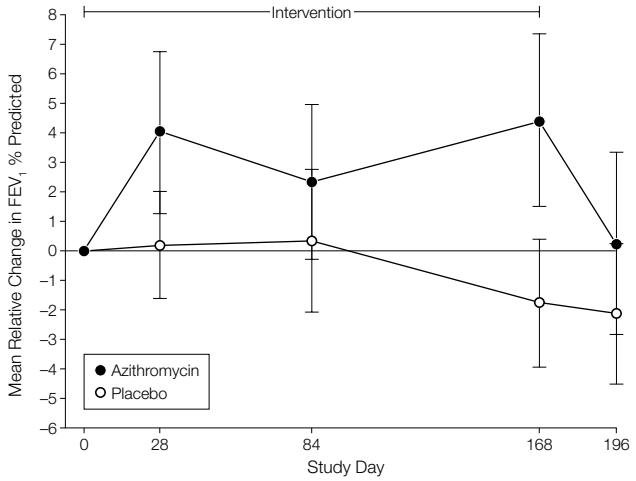
Inflammatory Markers

The mean (SD) elastase levels in the azithromycin and placebo groups were similar at baseline (1.9 [0.4] log µg/mL in both groups). The mean (SD) increase in elastase from day 0 to day 168 was 0 (0.5) log µg/mL in the azithromycin group compared with 0.2 (0.5) log µg/mL in the placebo group (mean difference, –0.2; 95% CI, –0.4 to 0; $P=.01$). The IL-8 levels were similar at baseline (5.2 [0.5] log pg/mL in both groups) and did not change significantly during the study (mean difference, –0.1; 95% CI, –0.3 to 0.1; $P=.14$).

COMMENT

Treatment of patients with CF chronically infected with *P aeruginosa* with azithromycin for 168 days (24 weeks) led to improvement in clinical param-

Figure 2. Mean Relative Change in FEV_1% Predicted



No. of Participants					
Azithromycin	87	87	87	84	81
Placebo	98	97	95	93	89

FEV_1 indicates forced expiratory volume in 1 second. Error bars indicate 95% confidence intervals.

Table 2. Most Frequently Occurring Adverse Events in Azithromycin vs Placebo Participants*

Adverse Event	No. of Participants (%) Azithromycin (n = 87)	Placebo (n = 98)	% Risk Difference (95% CI)
Cough	64 (74)	80 (82)	–8 (–20 to 4)
Sore throat	38 (44)	36 (37)	7 (–7 to 21)
Increased sputum	34 (39)	48 (49)	–10 (–24 to 4)
Nasal congestion	33 (38)	36 (37)	1 (–12 to 15)
Nausea	29 (33)	16 (16)	17 (5 to 29)†
Rhinorrhea	29 (33)	25 (26)	7 (–5 to 21)
Headache	28 (32)	31 (32)	0 (–13 to 14)
Abdominal pain	26 (30)	31 (32)	–2 (–15 to 12)
Fever	24 (28)	36 (37)	–9 (–22 to 4)
Fatigue	24 (28)	36 (37)	–9 (–22 to 4)
Dyspnea	23 (26)	24 (24)	2 (–10 to 15)
Diarrhea	20 (23)	8 (8)	15 (4 to 25)†
Pulmonary congestion	18 (21)	19 (19)	2 (–1 to 13)
Hemoptysis	17 (20)	25 (26)	–6 (–17 to 6)
Wheezing	15 (17)	4 (4)	13 (4 to 23)†
Dizziness (except vertigo)	14 (16)	9 (9)	7 (–3 to 17)
Vomiting	14 (16)	15 (15)	1 (–10 to 11)
Decreased lung function	13 (15)	7 (7)	8 (–1 to 17)
Decreased appetite	13 (15)	15 (15)	0 (–11 to 10)

Abbreviation: CI, confidence interval.
*Events that occurred during or after the first dose of study drug in at least 15% of all participants receiving azithromycin are provided with the corresponding frequency of occurrence in the placebo group.
†$P<.05$.

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eters associated with morbidity and mortality in CF.[27] Pulmonary function and nutritional status improved, pulmonary exacerbation rates decreased, and there was some evidence of improved quality of life. No unexpected adverse events were identified and the drug was generally well tolerated.

The concomitant medications recombinant human dornase alfa inhalation solution and tobramycin solution for inhalation were widely used by participants during this study. The results suggested that participants had clinical benefits when azithromycin was added to other therapies proven to be effective in patients with CF. In addition, the impact of azithromycin was comparable with that reported in previous studies of these and other CF therapies. In this trial, the relative change in FEV_1% predicted was 6.2% compared with the 5.6% and 11.0% treatment effects observed in studies of recombinant human dornase alfa and tobramycin solution for inhalation, respectively.[13,14]

This clinical trial of azithromycin expands on and confirms the trends observed in 2 other recently reported smaller trials that demonstrated a benefit from azithromycin in patients with CF.[7,8] Equi et al[7] performed a double-blind, placebo-controlled trial in England that included 41 children, 20 of whom did not have persistent infection with *P aeruginosa*, defined as 3 positive cultures during the year before the trial. The crossover design of this trial included a 2-month washout period between 2 6-month treatment phases. The median relative improvement in FEV_1% predicted between the azithromycin and placebo treatment phases was 5.4%. Oral antibiotic use was reduced but the number of pulmonary exacerbations and courses of intravenous antibiotics did not statistically differ between azithromycin and placebo treatment phases. No subjective reports of adverse effects were elicited. Wolter et al[8] conducted a randomized, double-blind, placebo-controlled trial in Australia in 60 stable adults with CF chronically infected with *P aeruginosa*. Because of the relatively small number of participants, treatment assignments resulted in significant differences between the azithromycin and placebo groups; at baseline, participants randomized to the azithromycin group had better lung function and were, on average, taller and heavier. These baseline differences required statistical adjustment for baseline FEV_1 in the analysis of efficacy. Nevertheless, the azithromycin group had a 3.6% relative improvement in FEV_1% predicted and the number of courses of intravenous antibiotics and hospital days were reduced. Despite differences in patient populations, study design, and

Table 3. Prevalence of Microorganisms at Baseline and Newly Detected at Day 168 in Participants With CF Treated With Azithromycin vs Placebo*

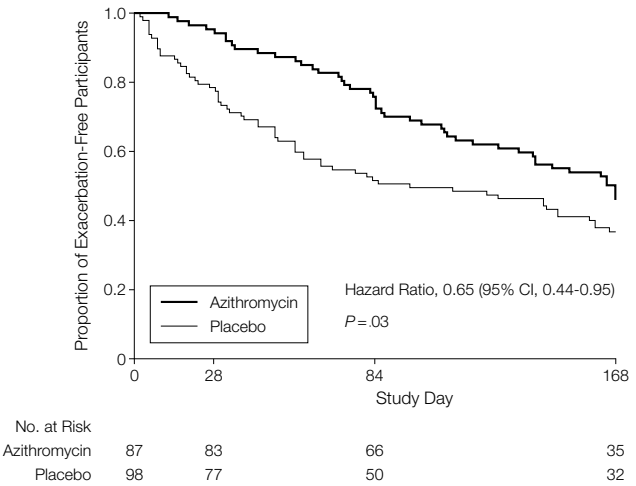
	No. of Participants (%)			
	Present at Screening		Newly Detected at Day 168	
Microorganism	Azithromycin (n = 87)	Placebo (n = 97)	Azithromcyin (n = 84)	Placebo (n = 92)
Pseudomonas aeruginosa				
Mucoid	77 (88.5)	89 (91.8)	2 (2.4)	5 (5.4)
Multidrug-resistant	1 (1.2)	0	1 (1.2)	0
Staphylococcus aureus	52 (59.8)	47 (48.5)	2 (2.4)	12 (13.0)
Methicillin-resistant *S aureus*	10 (11.5)	4 (4.1)	3 (3.6)	4 (4.4)
Nontuberculous mycobacteria	3 (5.1)†	5 (8.3)†	1 (2.4)‡	4 (12.5)‡
Burkholderia cepacia complex	0	1 (1.0)	1 (1.2)	0
Stenotrophomonas maltophilia	5 (5.8)	9 (9.3)	4 (4.8)	6 (6.5)
Achromobacter xylosoxidans	9 (10.3)	4 (4.1)	2 (2.4)	1 (1.1)
Aspergillus species	8 (9.2)	19 (19.6)	7 (8.3)	7 (7.6)

*Respiratory tract samples were available for baseline assessments in 87 participants (100%) in the azithromycin group and 97 (99%) of 98 participants in the placebo group. Respiratory tract samples were available at both baseline and day 168 for assessing newly detected pathogens from 84 (97%) participants in the azithromycin group and 92 (94%) participants in the placebo group.

†These participants had acid-fast bacillus smear negative results but nontuberculous mycobacteria grew from the screening culture. Study drug was discontinued when the culture results were available.

‡At day 168, only 43 participants in the azithromycin group and 38 participants in the placebo group had sufficient sputum to process for nontuberculous mycobacteria.

Figure 3. Proportion of Participants Remaining Exacerbation-Free at Study Day



Kaplan-Meier method estimates of the proportion of patients remaining exacerbation-free during the active treatment phase of the study. *P* value derived from Cox proportional hazards regression model.

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treatment regimens, all 3 trials demonstrated clinical improvement associated with azithromycin treatment. Our trial allowed us to more completely assess safety and evaluate several important secondary outcomes.

The mechanism of action of azithromycin in patients with CF has not been elucidated. In vitro data suggest that azithromycin has bactericidal activity against *P aeruginosa* in stationary phase growth,[28] but azithromycin had minimal effect on bacterial density in this trial. Although azithromycin has activity against *S aureus*, this pathogen was not eradicated. The relative importance of *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in patients with CF is uncertain and was not evaluated in this trial, but the beneficial effect of azithromycin is unlikely to be mediated solely by impact on these organisms. Macrolide antibiotics show a modest degree of in vitro synergy with antipseudomonal antibiotics against gram-negative organisms from patients with CF.[29] An anti-inflammatory mechanism of action has been suggested for macrolide antibiotics[30] but none of the clinical trials have shown statistically significant reductions in IL-8. The impact on neutrophil elastase noted in this trial was modest and of uncertain clinical significance. In the study by Wolter et al,[8] C-reactive protein declined in the azithromycin group but the C-reactive protein level was highly correlated with lung function as patients with normal C-reactive protein had better lung function. Macrolide antibiotics have been shown to decrease sputum viscosity[30,31] but this has not been systematically studied. We speculate that the increased wheezing reported by participants in the azithromycin group was because of increased mobilization of respiratory tract secretions. Future studies should assess changes in sputum rheology. Finally, a direct effect on the CF transmembrane conductance regulator has been postulated.[32]

The emergence of macrolide-resistant nontuberculous mycobacteria is of concern when considering chronic azithromycin therapy for patients with CF. In a multicenter study conducted in 1000 patients with CF aged 10 years or older, the prevalence of nontuberculous mycobacteria was approximately 12%, although many patients did not fulfill American Thoracic Society criteria for active disease.[33,34] Because of these concerns, potential participants in the azithromycin study were screened for nontuberculous mycobacteria. Physicians considering azithromycin therapy should assess patients with CF for nontuberculous mycobacteria before and every 6 months after initiating azithromycin.[23]

The results of this trial suggest several avenues for future research. Only 19 participants aged 6 to12 years were enrolled and therefore further investigations are needed in younger patients with CF infected with *P aeruginosa*. This study did not assess the efficacy of azithromycin in patients infected with *B cepacia* complex or uninfected with *P aeruginosa*. Evaluation of the effects and safety of azithromycin beyond 24 weeks is needed as the decline in lung function after discontinuing azithromycin suggests that sustained benefit could be derived from more prolonged therapy. The emergence of resistance to macrolide antibiotics in oral flora, potentially *S aureus*, and nontuberculous mycobacteria should be monitored during long-term therapy.

Despite the remaining questions, azithromycin is medication that is currently available. Care providers of patients with CF should consider this therapy for patients with CF aged 6 years or older and chronically infected with *P aeruginosa*.

Table 4. Hospitalizations and Antibiotic Use Among Participants Treated With Azithromycin vs Placebo*

	Azithromycin (n = 87)	Placebo (n = 98)	Difference (95% CI)	*P* Value
Hospitalization				
Participants hospitalized, No. (%)	14 (16)	29 (30)	−14 (−25 to −1)	.05
Hospital-days per study participant, mean (SD)	2.0 (5.8)	3.8 (8.3)	−1.8 (−3.9 to 3.0)	.09
IV antipseudomonal antibiotics				
Participants treated, No. (%)	18 (21)	30 (31)	10 (−22 to 3)	.17
Days per study participant, mean (SD)	4.2 (9.9)	6.9 (12.6)	−2.7 (−6.0 to 0.6)	.10
Oral quinolones				
Participants treated, No. (%)	39 (45)	57 (58)	−13 (−27 to 3)	.10
Days per study participant, mean (SD)	11.9 (21.5)	15.6 (18.0)	−3.7 (−9.4 to 2.0)	.21
Nonquinolone oral antibiotics				
Participants treated, No. (%)	21 (24)	34 (35)	−11 (−23 to 3)	.16
Days per study participant, mean (SD)	5.5 (13.7)	13.5 (31.4)	−8.0 (−15.2 to −0.8)	.03

Abbreviations: CI, confidence interval; IV, intravenous.
*All parameters were measured from day 0 to day 168.

Table 5. Change in Quality of Life Scores From Baseline to Day 168 for Participants Treated With Azithromycin vs Placebo

	Mean Change (SD)			
CF Quality of Life Questionnaire	Azithromycin (n = 85)	Placebo (n = 92)	Difference (95% CI)	*P* Value
Physical factor	0.8 (8.9)	−1.9 (8.8)	2.7 (0.1 to 5.3)	.05
Psychosocial factor	1.6 (12.1)	1.2 (10.9)	0.4 (−3.1 to 3.7)	.85
Body image factor	3.1 (14.5)	1.7 (14.8)	1.4 (−2.9 to 5.8)	.51
Total	1.7 (7.5)	−0.1 (7.5)	1.8 (−0.4 to 4.0)	.35

Abbreviation: CF, cystic fibrosis; CI, confidence interval.

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