ORIGINAL RESEARCH

Azithromycin for Bronchial Asthma in Adults: An Effectiveness Trial

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Background: **Macrolides have antimicrobial and anti-inflammatory properties that may be useful in the treatment of chronic asthma.**

Methods: **We performed a randomized, placebo-controlled, double-blinded effectiveness trial of 12 weekly doses of adjunctive azithromycin, with follow-up to 1 year after randomization, in adults with persistent asthma. Measurements included overall asthma symptoms, asthma quality of life (AQL), and asthma control. Eligible subjects who declined to participate in randomization were offered enrollment into a parallel open-label (OL) azithromycin treatment arm.**

Results: **Of 304 adult asthma patients screened, 97 (32%) were enrolled: 38 were randomized to azithromycin, 37 were randomized to placebo, and 22 opted in as OL subjects. OL subjects had higher rates of severe persistent asthma compared with randomized subjects (32% vs 8%, respectively; $P = .012$). At 1 year, compared with the placebo arm, subjects randomized to azithromycin were more likely to have an AQL score ≥1 unit increase compared with baseline, but this difference was not statistically significant (36% vs 21% for placebo; $P = .335$). Compared with placebo, OL subjects had significant improvements in overall asthma symptoms from baseline ($P = .0196$), AQL ($P = .0006$), and asthma control ($P = .0148$).**

Conclusions: **Adults with asthma who were randomized to azithromycin did not show statistically significant improvement in asthma outcomes, although the study was underpowered to detect clinical improvement in 15% (number needed to treat = 7). Adults with severe persistent asthma who elected OL treatment documented clinical improvements in asthma symptoms, AQL, and asthma control that persisted after completion of OL azithromycin (number needed to treat = 2). (J Am Board Fam Med 2012;25:442–459.)**

Keywords: **Antibiotics; Asthma; Clinical Trials, Randomized; Infectious Diseases; Practice-based Research Networks**

There is increasing interest in the therapeutic potential of macrolides in chronic asthma. A 2005 Cochrane review concluded that there was insufficient evidence to support or refute the use of macrolides in patients with chronic asthma and recommended further studies.[1] Potential macrolide mechanisms of action include nonantimicrobial effects,[2] antimicrobial activity targeting the respiratory pathogens *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, or both.[3]

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Current guideline-recommended asthma treatments have limited generalizability because of a lack of effectiveness trials of representative samples of asthma patients and because of the systematic exclusion of large numbers of asthma patients from the efficacy trials on which the guidelines are based. On average, 19 of 20 people with physician-diagnosed asthma were excluded from the clinical research[4,5] and more than half of adults with asthma may remain poorly controlled, even when they are treated.[6] Thus, it is important to test therapies for asthma in generalizable effectiveness trials.

We therefore conducted a primary care, practice-based effectiveness trial designed to include 3 months of adjunctive treatment (in addition to usual care) with the azalide macrolide azithromycin followed by a 9-month observational period after treatment. The goal of our trial, AZithroMycin-Asthma Trial In Community Settings (AZMATICS), was to investigate whether azithromycin has value for patients with persistent asthma in reducing the severity of their symptoms over time.

Methods

Adults with persistent asthma symptoms as defined by current guidelines[7] were randomized to receive 12 weekly doses of azithromycin or placebo as adjunctive therapy between June 2006 and November 2009. Self-reported questionnaire data were collected for 1 year after randomization. Patients were recruited and enrolled from community practice-

Table 1. Inclusion, Exclusion, and Outcome Criteria

	Criteria
Inclusions	• Adults ≥18 years of age with physician-diagnosed asthma (symptomatic ≥2 days per week and/or ≥2 nights per month or in exacerbation)
	• Objective evidence for reversible airway obstruction (≥12% and ≥200 mL change in FEV_1[8] and/or a 25% and 60 L/min change in PEFR[9]) either spontaneously or after treatment
	• Asthma for at least 6 months before enrollment
Exclusions	• Not English literate or has no email address or Internet access
	• Macrolide allergy
	• Pregnant or lactating
	• ≥4 weeks of continuous use of macrolides, tetracyclines, or quinolones within 6 months of randomization
	• Asthma symptoms less than 6 months' duration
	• Unstable asthma requiring immediate emergency care
	• Comorbidities likely to interfere with study assessments or follow-up (eg, cystic fibrosis, obstructive sleep apnea requiring CPAP, cardiomyopathy, congestive heart failure, terminal cancer, alcohol or other drug abuse, or any other serious medical condition that, in the opinion of the study physician, would seriously interfere with or preclude assessment of study outcomes or completion of study assessments)
	• Medical conditions for which macrolide administration may possibly be hazardous (eg, acute or chronic hepatitis, cirrhosis, or other liver disease; chronic kidney disease; or history of prolonged cardiac repolarization and QT interval or *torsades de pointes*).
	• Specified medications for which close monitoring has been recommended in the setting of macrolide administration (digoxin, theophylline, warfarin, ergotamine or dihydroergotamine, triazolam, carbamazepine, cyclosporine, hexobarbital, or phenytoin)
Outcomes	• Asthma symptom scores (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = worst ever) within the past 24 hours; every 1.5 months
	• AQL (Juniper AQL questionnaire)[10] within the past 2 weeks; every 3 months
	• Asthma control (mini-Juniper Asthma Control Questionnaire, without pulmonary function)[11,12] within the past week; every 3 months
	• Exacerbations (a steroid burst, an unscheduled or emergency visit and/or a hospitalizations for asthma) within the past 1.5 months; every 1.5 months
	• Other respiratory illnesses within the past 1.5 months; every 1.5 months
	• Off-study antibiotic use within the past 1.5 months; every 1.5 months
	• Adverse events within the past 1.5 months; every 1.5 months
	• Use of asthma-controller medications (oral or inhaled steroids, LABAs, or antileukotriene agents) within the past 3 months; every 3 months
	• Self-reported improvement in asthma (compared with baseline) within the past 3 months; every 3 months

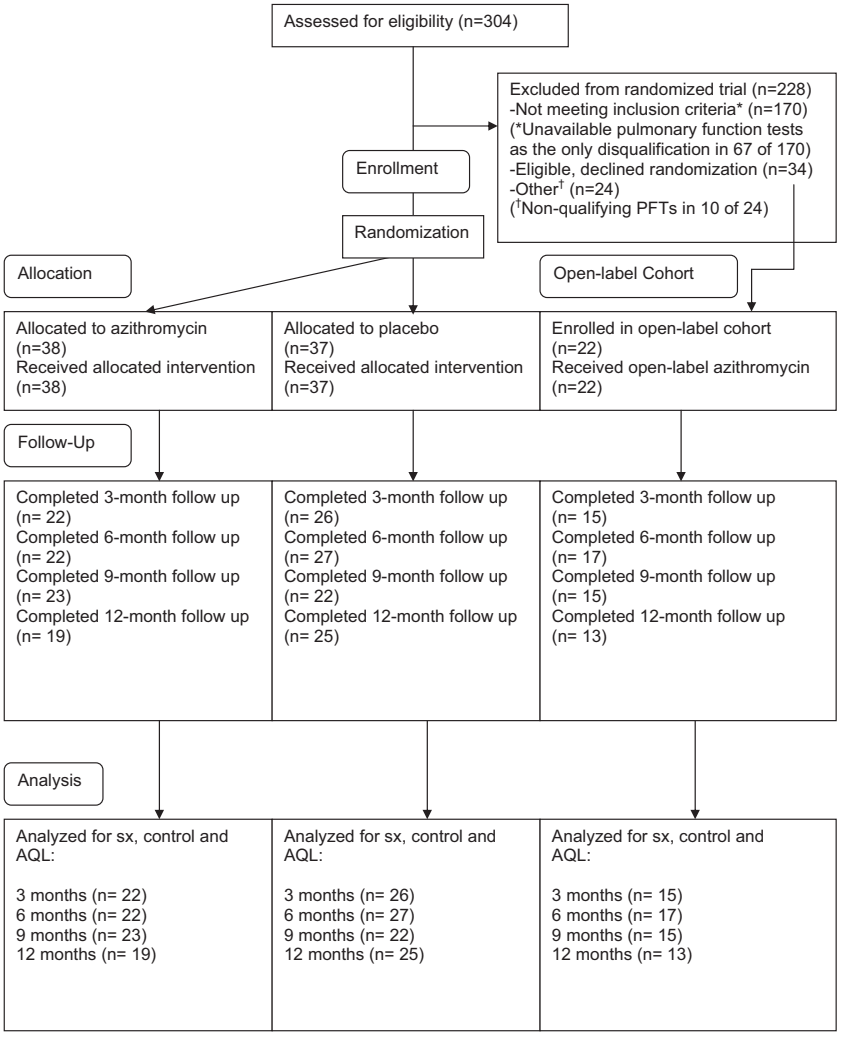
AQL, asthma quality of life; CPAP, continuous positive airway pressure; FEV_1, forced expiratory volume in 1 second; LABA, long-acting bronchodilators; PEFR, peak expiratory flow rate.

based settings throughout North America. Study clinician members and/or staff of 5 practice-based research networks (PBRNs) and one community-based allergist enrolled patients from their practices for this study. The PBRNs included one nationwide network (American Academy of Family Physicians National Research Network) and 4 regional networks (Ambulatory Network for Scholarship and Research, Illinois; Cleveland Ambulatory Research Network, Ohio; Oklahoma Physicians Resource/Research Network; and the Wisconsin Research and Education Network). Further participant details are provided in the Acknowledgments. During this "real-world" study, we encountered eligible patients, most of whom had severe treatment-resistant or refractory asthma, who declined randomization in favor of being treated with azithromycin. Rather than exclude these patients entirely, we elected to enroll them as a parallel observational cohort. Patients who opted to participate in this "open-label" (OL) arm received a prescription for azithromycin from their personal physician and were followed for the same outcomes as the randomized arm.

Study Eligibility

Eligibility criteria can be found in Table 1. Community-based clinicians enrolled and randomized eligible patients and remained available to assess side effects or severe adverse reactions, but they were not involved in follow-up data collection. All subjects continued to receive usual asthma care from their doctor. All study sites received approval

Figure 1. CONSORT diagram. *Unavailable pulmonary function tests (PFTs) as the only disqualification of 67 of 170. †Nonqualifying PFTs in 10 of 24.



from their respective human subject committees, and subjects provided written, informed consent.

Randomization and Masking

An independent statistician prepared the randomization codes used for subject assignment to the azithromycin or placebo study arms. The investigators, study subjects, and study site personnel were blinded to treatment allocation. Study medication was azithromycin 600 mg, 1 tablet daily for 3 days followed by 1 tablet weekly for 11 weeks, or identical matching placebo tablets. Each study site

Table 2. Patient Characteristics

Characteristic	Randomized Placebo (n=37)	Randomized Azithromycin (n=38)	Open-Label Azithromycin (n=22)	*P**
Age(years), mean(SD)	47.4 (14.2)	45.7 (15.5)	45.4 (15.2)	.621/.745
At asthma diagnosis	24 (<1–59)	24 (<1–58)	28 (11–59)	.603/.104
Diagnosis at age ≥18 years	21 (57)	24 (63)	19 (86)	.641/.023
Male sex	13 (35)	11 (29)	12 (55)	.626/.078
Smoking status				.187/.028
Never	13 (35)	20 (53)	16 (73)	
Former	19 (51)	12 (32)	6 (27)	
Current	5 (14)	6 (16)	0 (0)	
White race	33 (89)	36 (95)	18 (82)	.430/.227
Education, median years (range)	15 (10–20)	14 (12–22)	17 (12–25)	.550/<.001
≥High school graduate	35 (95)	38 (100)	21 (100)	.240/1.000
Chronic sinusitis	11 (30)	14 (37)	17 (77)	.626/<.001
Atopy				
Allergy tested	18 (53)	18 (49)	19 (86)	.814/.003
Negative	2 (11)	1 (6)	6 (32)	.759/.003
Positive for 1–3 positive	4 (22)	3 (17)	8 (42)	
Positive for ≥4	12 (67)	14 (78)	5 (26)	
Infectious asthma†	6 (16)	17 (46)	13 (59)	.011/.024
Exacerbations (previous 2 years), n (%)	24 (65)	26 (68)	14 (64)	.809/.802
Hospitalized	0 (0)	2 (5)	4 (18)	.493/.023
Emergency visit	14 (38)	19 (50)	9 (41)	.355/1.000
Steroid burst	22 (59)	24 (63)	13 (59)	.815/1.000
Baseline asthma severity, n (%)				
Day symptom frequency‡				.675/.009
Mild to moderate	35 (95)	34 (89)	15 (68)	
Severe	2 (5)	4 (11)	7 (32)	
Night symptom frequency‡				1.000/.046
Mild to moderate	33 (89)	33 (87)	15 (68)	
Severe	4 (11)	5 (13)	7 (32)	
Coexisting COPD	8 (22)	5 (13)	2 (9)	.375/.509
Lung function, mean (SD)				
FEV_1, L (n)	18	19	7	
Low§	2.24 (1.25)	2.33 (1.05)	2.48 (1.19)	.812/.688
% Change‖	42 (47.4)	26 (25.9)	33 (26.8)	.214/.969
PEFR, L/min (n with value)	25	25	18	
Low§	258 (110)	276 (110)	300 (105)	.566/.281
% Change‖	62 (56)	63 (49)	85 (63)	.927/.140
Any controller medication	33 (89)	25 (66)	19 (86)	.026/.549
Inhaled corticosteroid	30 (81)	24 (63)	18 (82)	
Long-acting bronchodilator¶	26 (70)	14 (37)	15 (68)	
Leukotriene inhibitor	8 (22)	9 (24)	6 (27)	
Oral prednisone	4 (11)	2 (5)	1 (5)	

Continued

Table 2. Continued

Characteristic	Randomized Placebo (n=37)	Randomized Azithromycin (n=38)	Open-Label Azithromycin (n=22)	*P**
Baseline asthma measures, mean (SD)**				
Overall asthma symptoms	1.48 (0.94)	1.42 (0.77)	2.06 (0.73)	.744/.005
Asthma quality of life	4.97 (1.28)	4.98 (1.27)	4.12 (1.29)	.988/.023
Asthma control	1.56 (1.02)	1.75 (0.93)	2.26 (1.35)	.424/.090

Values provided as n (%) unless otherwise indicated.
*P values comparing randomized placebo versus randomized azithromycin/randomized cohort versus open-label cohort.
†History showed first asthma symptoms began after an acute respiratory illness.
‡Day: mild = ≥2 days/week to less than daily; moderate = ≥1 per day to less than continuous; severe = continuous. Night: mild = ≥2 per month to ≤1 per week; moderate = >1 per week to ≤1 per night; severe = >1 per night.
§Before bronchodilator use or lowest spontaneous value.
‖Based on data after bronchodilator use or highest spontaneous value. Some subjects had either FEV_1 or PEFR values, not both.
¶All subjects using a long-acting bronchodilator also were using an inhaled corticosteroid.
**See Methods for definitions.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate.

received coded study medication bottles (1:1 allocation) in blocks of 6 and was instructed to distribute them (numbered 1 to 6) in numerical ascending order to eligible consenting study subjects. After 3 weeks of taking study medication, subjects were asked to guess their allocation.

Open-Label Treatment

Internet trial registration (http://clinicaltrials.gov/show/NCT00266851) and another Internet site (http://asthmastory.com) identified asthma patients wanting to participate in AZMATICS.[13] When they learned that they had a 50% chance of receiving a placebo, many of these patients declined to be randomized but remained interested in the use of azithromycin for treatment of their asthma. Institutional review board approval was obtained to enter eligible subjects requesting azithromycin into a parallel, OL observational cohort. OL subjects obtained a 12-week prescription for weekly azithromycin from their personal physician and were monitored for the same baseline and outcome data that were being collected for the randomized cohort. Because 600-mg azithromycin tablets were not uniformly available, OL treatment consisted of 2 azithromycin tablets (250 mg each), to achieve a 500-mg daily dose for 3 days, followed by 3 tablets to achieve a 750-mg, once-weekly dose for 11 additional weeks.

Study Outcomes

Subjects submitted follow-up data via Internet questionnaires. During the first 3 months after randomization (the study medication administration period), subjects reported weekly via the Internet whether they had taken their assigned study medication during the previous week. In addition to study medication adherence, subjects also reported weekly on side effects for the first 3 months. Outcome data were recorded every 1.5 months (6 weeks) through 12 months. Outcome measures are listed in Table 1.

Statistical Analysis

All analyses were by intention to treat, and no subjects with available data were excluded from any analysis. Repeated-measures (RM) analysis of variance (ANOVA)—with intervention and time as fixed effects; subjects as random effects; and age, sex, and ever-smoking as covariates—was conducted for each of the continuous variables. After finding significant effects in the RM ANOVA models, we explored the effects with tests at specific time points. We used Fisher exact test for categorical variables, Wilcoxon rank sum tests for continuous variables (reported as median and range), and t tests for continuous variables (reported as mean and standard deviation). We controlled for the effects of age, sex, ever-smoking, and asthma controller medication using ANOVA for normally distributed continuous outcomes and logistic regression for binary outcomes. On the basis of our pilot results, a total sample size of 58 had 80% power (for $\alpha = 0.05$) to detect a 0.66-unit (13%) difference in overall asthma symptoms (the primary outcome). AZMATICS used a Data Safety Monitoring

Board that met approximately every 6 months. The Data Safety Monitoring Board did not identify any reason for early termination.

Results

Screening and Enrollment

Of 304 adult asthma patients screened, 97 (32%) were enrolled (38 were randomized to azithromycin, 37 were randomized to placebo, and 22 elected OL treatment). An additional 67 of 304 screened patients (22%) who were otherwise eligible lacked pulmonary function data and could not complete the screening process (Figure 1).

Adherence

Self-reported mean adherence to taking azithromycin or placebo ranged from 96% to 99%, with no significant differences among the 3 study groups ($P = .706$). Adherence to reporting follow-up data ranged from 63 of 97 participants (65%) at 12 weeks to 57 participants (59%) at 48 weeks, with no

Figure 2. Differences from baseline for asthma symptoms, quality of life, and control. A: Symptoms—rating of overall asthma symptoms for the past 24 hours (negative numbers indicate decreased symptoms and hence improvement). B: Quality of life—Juniper Asthma Quality of Life Questionnaire (AQLQ); positive numbers indicate higher quality of life scores and hence improvement). C: Control—Juniper Mini-Asthma Control Questionnaire (ACQ; negative numbers indicate better control and hence improvement). See Methods for details. Symbols represent the mean paired differences from baseline. Bars represent 95% confidence intervals. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$ (t tests, placebo versus open label).

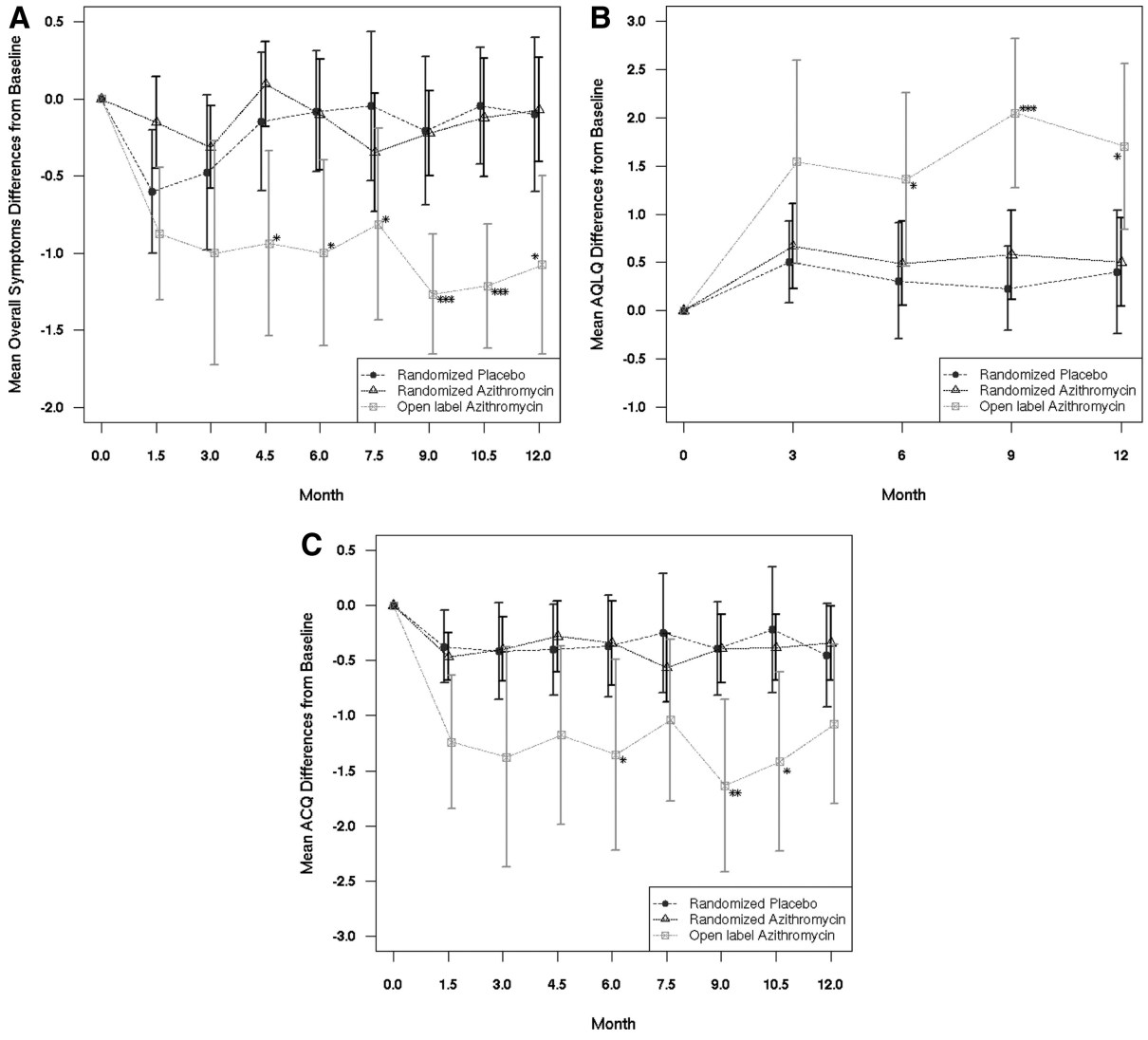


Table 3. Asthma Outcomes*

	Randomized Placebo	Randomized Azithromycin	Open-label Azithromycin	*P*, Placebo vs Randomized Azithromycin	*P*, Placebo vs Open-Label
Change in overall asthma symptoms, from baseline					
Week 6	−0.60 (1.07) (n=30)	−0.15 (0.83) (n=33)	−0.88 (0.81) (n=16)	.071/.071†	.333/.428†
Week 12	−0.48 (1.16) (n=23)	−0.31 ((0.74) (n=32)	−1.0 (1.37) (n=16)	.551/.580†	.223/.723†
Week 18	−0.15 (1.13) (n=27)	0.10 (0.75) (n=31)	−0.94 (1.12) (n=16)	.344/.178†	.034/.161†
Week 24	−0.08 (0.95) (n=25)	−0.10 (0.96) (n=30)	−1.0 (1.17) (n=17)	.939/.599†	.012/.013†
Week 30	−0.05 (1.09) (n=22)	−0.34 (1.01) (n=29)	−0.81 (1.17) (n=16)	.322/.280†	.048/.870†
Week 36	−0.21 (1.14) (n=24)	−0.22 (0.70) (n=27)	−1.27 (0.70) (n=15)	.959/.942†	.001/.017†
Week 42	−0.04 (0.88) (n=23)	−0.12 (0.93) (n=25)	−1.21 (0.70) (n=14)	.770/.858†	<.001/.001†
Week 48	−0.10 (1.07) (n=20)	−0.07 (0.88) (n=29)	−1.07 (0.95) (n=13)	.916/.758†	.011/.067†
Change in AQL, from baseline					
Week 12	0.50 (0.95) (n=22)	0.67 (1.10) (n=26)	1.54 (1.91) (n=15)	.584/.682†	.067/.180†
Week 24	0.31 (1.36) (n=22)	0.49 (1.11) (n=27)	1.36 (1.75) (n=17)	.618/.382†	.049/.151†
Week 36	0.23 (1.02) (n=23)	0.58 (1.04) (n=22)	2.05 (1.40) (n=15)	.261/.342†	<.001/.001†
Week 48	0.40 (1.33) (n=19)	0.50 (1.10) (n=25)	1.70 (1.42) (n=13)	.784/.929†	.015/.068†
Change in asthma control, from baseline					
Week 6	−0.37 (0.88) (n=30)	−0.46 (0.60) (n=33)	−1.24 (1.14) (n=16)	.634/.654†	.014/.009†
Week 12	−0.41 (1.01) (n=23)	−0.40 (0.80) (n=32)	−1.38 (1.87) (n=16)	.946/.998†	.075/.324†
Week 18	−0.40 (1.05) (n=27)	−0.28 (0.88) (n=31)	−1.18 (1.53) (n=16)	.637/.573†	.085/.179†
Week 24	−0.37 (1.12) (n=25)	−0.34 (1.03) (n=30)	−1.35 (1.69) (n=17)	.925/.536†	.045/.034†
Week 30	−0.25 (1.22) (n=22)	−0.56 (0.81) (n=29)	−1.04 (1.38) (n=16)	.307/.281†	.078/.163†
Week 36	−0.39 (1.00) (n=24)	−0.39 (0.79) (n=27)	−1.63 (1.41) (n=15)	1.000/.852†	.007/.015†
Week 42	−0.22 (1.32) (n=23)	−0.38 (0.72) (n=25)	−1.42 (1.41) (n=14)	.604/.817†	.016/.068†
Week 48	−0.45 (1.00) (n=20)	−0.34 (0.88) (n=29)	−1.08 (1.20) (n=13)	.692/.525†	.132/.379†
AQL improved ≥1 unit, n/N (%)					
Week 12	5/22 (23)	11/26 (42)	9/15 (60)	.221/.136‡	.038/.098‡
Week 24	6/22 (27)	8/27 (30)	11/17 (65)	1.000/.745‡	.026/.048‡
Week 36	5/23 (22)	6/22 (27)	12/15 (80)	.738/.738‡	.001/.003‡
Week 48	4/19 (21)	9/25 (36)	7/13 (54)	.335/.386‡	.072/.116‡
Asthma control improved ≥1 unit, n/N (%)					
Week 6	6/30 (20)	4/33 (12)	9/16 (56)	.498 /.421‡	.021/.010‡
Week 12	7/23 (30)	7/32 (22)	11/16 (69)	.539/.531‡	.025/.045‡
Week 18	7/27 (26)	4/31 (13)	9/16 (56)	.315/.437‡	.059/.054‡
Week 24	6/25 (24)	10/30 (33)	10/17 (59)	.556/.144‡	.029/.017‡
Week 30	5/22 (23)	9/29 (31)	8/16 (50)	.546/.502‡	.098/.105‡
Week 36	5/24 (21)	6/27 (22)	10/15 (67)	1.000/.875‡	.007/.009‡
Week 42	6/23 (26)	7/25 (28)	8/14 (57)	1.000/.862‡	.085/.152‡
Week 48	5/20 (25)	8/29 (28)	5/13 (38)	1.000/.980‡	.461/.998‡

All values are mean (SD) unless otherwise indicated.

*See Methods for definitions.

†Univariate (*t* test)/multivariate (analysis of variance); controlled for age, sex, and ever-smoking at each time point, as well as for controller medication use at weeks 12, 24, 36, and 48 (controller data is unavailable for other time points).

‡Univariate (Fisher exact test)/multivariate (logistic regression); controlled for age, sex, and ever-smoking at each time point, as well as for controller medication use at weeks 12, 24, 36, and 48 (controller data is unavailable for other time points).

AQL, asthma quality of life.

significant differences between study groups (P = .122).

Baseline Characteristics

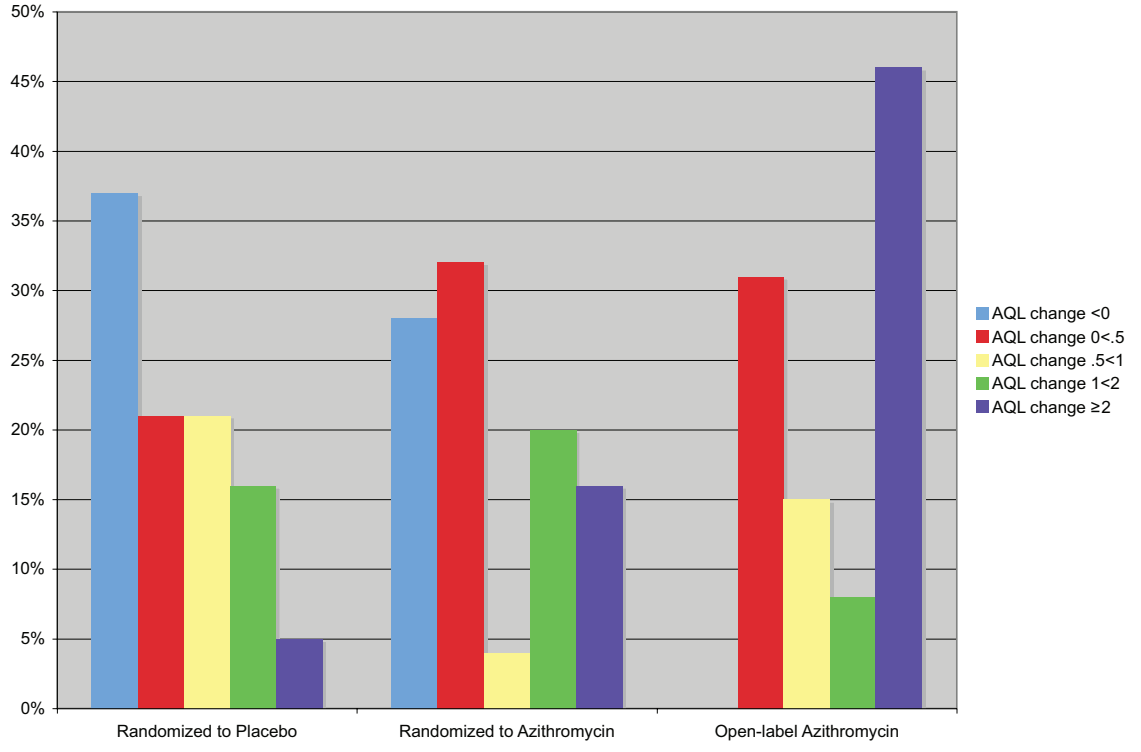
Table 2 presents the patient characteristics. The study group was mostly white and non-Hispanic with a high school education or greater and a broad range of age at asthma onset. The randomized groups were well balanced in major baseline characteristics (age, sex, smoking status, education, and asthma severity), but the group randomized to azithromycin reported more asthma onset after an acute respiratory illness ("infectious asthma") and less use of controller medication compared with the placebo group. Compared with the randomized groups, the OL cohort had significantly greater asthma severity at baseline (more hospitalizations for asthma, greater day and night symptom frequency, worse overall asthma symptoms, and worse asthma quality of life [AQL]); more adult-onset asthma; more chronic sinusitis; more allergy testing (but fewer positive tests); and more infectious asthma. Of the baseline covariates in RM ANOVAs, smoking was significantly associated with worse symptoms, AQL, and asthma control ($P < .05$ for each); older age was significantly associated only with worse AQL ($P < .05$), and sex was not significant in any analysis.

Outcomes

Randomized Trial

After 3 weeks of receiving study medication, 13% of those randomized to placebo and 29% randomized to azithromycin correctly guessed their allocation; 34% of placebo and 29% of azithromycin subjects guessed incorrectly, and the remainder were unsure of their allocation (P = .27). Subjects

Figure 3. Improvement in asthma quality of life (AQL) after azithromycin treatment may be "all or none." AQL change scores from baseline to 12 months after enrollment (9 months after treatment completion) are defined as follows: "AQL change <0" = AQL change worse than baseline; "AQL change 0 < .5" = change between 0 to <.5 units; "AQL change 0.5 < 1" = change between 0.5 to <1 (change of 0.5 unit is considered the minimum clinically important change); "AQL change 1 < 2" = change between 1 and 2 (change >1.5 units represents a large change); "AQL change ≥2" = change of 2 units or more. The contrasting patterns between placebo and open-label azithromycin were statistically significant, as noted in the text. The differences between randomized azithromycin and placebo were not statistically significant, as noted in the text.



randomized to azithromycin or placebo had no significant differences in overall asthma symptoms, AQL, or asthma control (Figure 2 and Table 3). At 1 year, subjects randomized to azithromycin were more likely than placebo subjects to have an AQL score ≥1-unit increase compared with baseline (36% vs 21%). This difference was not statistically significant ($P = .335$). Compared with subjects randomized by PBRN members (n = 69), subjects randomized by the community allergist (n = 6) were more likely to have been skin tested (49% of PBRN subjects skin tested vs 100% of allergist subjects; $P = .024$) but otherwise were similar in baseline characteristics, including comparable distribution of skin test results. Removing the allergist-recruited subjects from the RM ANOVA did not alter the outcome results (data not shown).

Open-Label Cohort

Comparing the OL and placebo groups, RM ANOVA found that the effect of intervention and the interaction of intervention and time were significant for symptoms, AQL, and asthma control ($P < .05$ for each). In univariate analyses, OL group asthma symptoms were significantly improved from month 4.5 to month 12 compared with placebo and AQL was significantly improved from month 6 to month 12, whereas asthma control

Table 4. Side Effects*

Side Effects, n (%)	Randomized Placebo	Randomized Azithromycin	Open-Label Azithromycin	$P^{\dagger}$
Nausea				.016/.008/.458
None	31 (91)	25 (71)	12 (60)	
Mild to moderate	1 (3)	9 (26)	6 (30)	
Severe	2 (6)	1 (3)	2 (10)	
Vomiting				1.000/.128/.456
None	32 (94)	33 (94)	18 (90)	
Mild to moderate	0 (0)	1 (3)	2 (10)	
Severe	2 (6)	1 (3)	0 (0)	
Stomach pain				.076/.001/.196
None	30 (88)	24 (69)	9 (45)	
Mild to moderate	3 (9)	10 (29)	10 (50)	
Severe	1 (3)	1 (3)	1 (5)	
Diarrhea				.106/.002/.196
None	29 (85)	23 (66)	9 (45)	
Mild to moderate	3 (9)	10 (29)	10 (50)	
Severe	2 (6)	2 (6)	1 (5)	
Rash				.743/.046/.420
None	33 (97)	33 (94)	16 (80)	
Mild to moderate	0 (0)	2 (6)	3 (15)	
Severe	1 (3)	1 (3)	1 (5)	
Swelling				.239/.716/.128
None	32 (94)	35 (100)	18 (90)	
Mild to moderate	1 (3)	0 (0)	2 (10)	
Severe	1 (3)	0 (0)	0 (0)	
Hearing loss				.743/1.000/.999
None	32 (94)	34 (97)	19 (95)	
Mild to moderate	1 (3)	1 (3)	1 (5)	
Severe	1 (3)	0 (0)	0 (0)	
Vaginal candidiasis				.670/1.000/.999
None	20 (91)	21 (84)	7 (88)	
Mild to moderate	3 (9)	4 (16)	1 (13)	
Severe	0 (0)	0 (0)	0 (0)	

*Worst reported severity during the 12-week treatment period.
†Fisher exact tests: randomized placebo versus randomized azithromycin/randomized placebo versus open-label azithromycin/randomized azithromycin versus open-label azithromycin.

Table 5. Randomized Trials of Second-Generation Macrolides/Azalides for Asthma: Study Designs

Reference	Age Group	Sampling Frame	Asthma Severity	Subjects (n)	Design	R_X/Duration	Observation after R_X
Shoji (1999)[17]	Adults	Hospital asthma clinic	Mild/moderate Aspirin-intolerant asthma	14	Single site; double-blind cross-over (4-week washout)	Roxithromycin, 300 mg daily or placebo/8 weeks	None
Amayasu (2000)[18]	Adults	Not stated (hospital asthma clinic[s]?)	Mild/moderate	17	Single site; double-blind cross-over (4-week washout)	Clarithromycin, 200 mg daily or placebo/8 weeks	None
Black (2001)[19]	18–60 years old	Majority of subjects recruited from the general population; recruitment method(s) not specified	Moderate/severe	232	Multinational; double-blind, parallel groups (Australia, New Zealand, Italy, Argentina)	Roxithromycin, 300 mg daily or placebo/6 weeks	24 weeks
Kraft (2002)[20]	Young adults	Subjects recruited from the general population via advertising	Not stated Mean FEV_1%pred = 69.3 35% were taking ICS	52	Single site; double-blind parallel groups All subjects underwent bronchoscopy before and after prescription	Clarithromycin, 1000 mg daily or placebo/6 weeks	None
Kostadima (2004)[21]	18–70 years old	Not stated (referral speciality setting)	Not stated, probably mild Mean FEV_1%pred ~85% Subjects using albuterol >2 times weekly were excluded	63	Single site; double-blind, parallel groups	Clarithromycin, 500 or 750 mg daily or placebo/8 weeks	None
Hahn (2006)[22]	≥18 years old	Community-based healthcare settings	Mostly mild/moderate	46	Multisite; double-blind, parallel groups	Azithromycin, 600 mg daily for 3 days then 600 mg weekly or placebo/6 weeks	12 weeks
Piacentini (2007)[23]	Children	Inpatient setting	Not stated	16	Single site; double-blind, parallel groups	Azithromycin, 10 mg/kg/day for 3 of 7 days or placebo/8 weeks	None
Simpson (2008)[24]	Adults	Specialty outpatient clinic	Severe refractory	45	Single site; double-blind, parallel groups Stratified by high (>61%)/low induced sputum neutrophil proportion	Clarithromycin, 1000 mg daily or placebo/8 weeks	4 weeks
Strunk (2008)[25]	Children	Academic asthma centers	Moderate/severe	55	Multisite; double-blind, parallel groups This was a study of macrolide as a "steroid-sparing" agent, not as an antimicrobial	Azithromycin, 250–500 mg daily or montelukast 5–10 mg daily of placebo/24 weeks	6 weeks

Continued

Table 5. Continued

Reference	Age Group	Sampling Frame	Asthma Severity	Subjects (n)	Design	R_X/Duration	Observation after R_X
Sutherland (2010)[26]	18–60 years old	Academic asthma centers	Suboptimally controlled asthma	92	Multisite; double-blind, parallel groups Stratified on Mpn or Cpn PCR± (bronchoscopic sampling) The study was underpowered to test PCR+ cases	Clarithromycin, 1000 mg daily or placebo/16 weeks	None
Hahn (2012), current study	≥18 years old	Community-based healthcare settings	Mild/moderate (randomized) Severe (open-label)	75 randomized 22 open-label	Multisite; double-blind, parallel groups	Azithromycin, 600 mg daily for 3 days then 600 mg weekly or placebo/12 weeks	36 weeks

%pred, percent of the predicted value; Cpn, *Chlamydia pneumoniae*; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; Mpn, *Mycoplasma pneumoniae*; PCR, polymerase chain reaction.

improvements were less consistent (Figure 2). In multivariate analyses (controlled for age, sex, ever-smoking, and concurrent controller medication use) the OL group reported significant improvements in symptoms, AQL, and asthma control that were maximal at study month 9 and waned somewhat at month 12 (Table 3).

AQL score change of 1 unit or more was a prespecified secondary outcome. AQL ≥ 1-unit improvement was achieved significantly more often in OL than in placebo subjects at the 3-, 6-, and 9-month time points. A similar but less consistent pattern was noted for asthma control scores with a ≥1-unit improvement (Table 3). After adjustment for age, sex, ever-smoking, and asthma controller medication use at 9 months (6 months after treatment completion), 80% of OL patients versus 22% of those enrolled in the placebo arm reported AQL score changes of ≥1-unit improvement ($P = .001$; number needed to treat [NNT] = 2) and 67% versus 21% reported asthma control score changes of ≥1-unit improvement ($P = .023$; NNT = 3). AQL and asthma control score improvements of ≥1 unit also were correlated significantly with self-reported asthma improvement at all time points ($P < .01$ for each).

We performed further exploratory analyses of different increments of change in AQL score up to and including a change of ≥2 units (Figure 3). The results showed that changes in AQL after azithromycin (both randomized or OL) assumed U-shaped distributions, whereas changes in AQL for placebo were skewed to the left, suggesting a binary "all or none" response to azithromycin. Finding patient characteristics that predict a treatment response are potentially important. Other than asthma severity, however, our data yielded no indications that patients' clinical characteristics were predictive of an azithromycin treatment response. For example, we analyzed OL and placebo subjects in a logistic model of AQL change of ≥2 units from baseline as the dependent variable and included age, sex, smoking status, and "infectious asthma" as other possible predictors. In this model, only azithromycin treatment was a significant predictor of AQL ≥2 ($P = .026$).

Exacerbations

This study was not powered to detect significant differences in exacerbation frequency. During the 12-month study period, 51% of subjects reported one or more asthma exacerbations. There were no

significant differences between the 3 study groups in exacerbation frequency at any time point or cumulatively.

Serious Adverse Events and Side Effects

One subject allocated to placebo was hospitalized for acute coronary syndrome. Another subject

Table 6. Randomized Trials of Second-Generation Macrolides/Azalides for Asthma: Exclusions, Outcomes, and Results

Reference	Exclusions*	Outcomes Reported	Results of Macrolide Treatment
Shoji (1999)[17]	Smokers	Blood eosinophils and ECP	Decreased eosinophils/ECP
	Controller medication	Sputum cell counts and ECP	Decreased eosinophils/ECP
			(No differences in sputum neutrophils)
		Sulpyrine provocation test	Not improved
			(No patient-oriented outcomes reported)
Amayasu (2000)[18]	Smokers	Blood eosinophils and ECP	Decreased eosinophils/ECP
	Aspirin sensitivity	Sputum cell counts and ECP	Decreased eosinophils/ECP
	ARI for 6 weeks	BHR	Improved
	Any asthma controller medication	Pulmonary function	Not improved
		Overall asthma symptoms	Improved
Black (2001)[19]	FEV_1 <50% predicted	Pulmonary function(PEF)	Improvement at end of prescription that waned after prescription
	C. pneumoniae IgG < 1:64 and IgA < 1:16	Pulmonary function(FEV_1)	Not improved
	Smoking ≥20 pack-years	Asthma symptoms	Not improved
	Bronchiectasis	AQL	Not improved
	Prednisone burst in previous month		
	Respiratory illness		
Kraft (2002)[20]	Smoking >5 pack years	PCR+ for Mpn or Cpn	31 of 55 were PCR+ for Mpn and/or Cpn
	Any cigarette within 2 years	Pulmonary function	Improved FEV_1 in PCR+ subject subgroup
	Any lung comorbidity	Lung inflammation	Decreased inflammatory cytokines
	Any LRTi within 3 months		(No patient-oriented outcomes reported)
Kostadima (2004)[21]	Asthma diagnosis <1 year ago	BHR	Decreased BHR
	Not on ICS	Pulmonary function	Not improved
	Rescue inhaler >2 times weekly	Serum free cortisol	Not affected
	Any smoking history		(No patient-oriented outcomes reported)
	Any other medication		
	FEV_1 < 50% predicted		
	Any ARI or exacerbation within 4 weeks before or during the study		
Hahn (2006)[22]	None	AQL	No improvement
		Rescue medication use	No improvement
		Cpn IgG and IgA antibodies	Baseline IgA predicted worsening symptoms
		Overall asthma symptoms	Improved at end of prescription and persisted after prescription
Piacentini (2007)[23]	Oral steroids in the preceding 3 months or during the study	Lung function	No improvement
	Signs of airway infection in the preceding month or during the study	BHR	Improved
		Lung inflammation	Reduced induced sputum neutrophils

Continued

Table 6. Continued

Reference	Exclusions*	Outcomes Reported	Results of Macrolide Treatment
Simpson (2008)[24]	Current smoking	Sputum inflammatory markers	Decreased airway IL-8 and neutrophils
	History of smoking, >5 pack-years	Pulmonary function	No improvement
	Antihistamine medication	BHR	No improvement
		Asthma control	No improvement
		Asthma symptoms	Decreased wheezing after prescription
		AQL	Improved (NNT = 6 for ≥0.5 units improvement)
			It was unclear whether the AQL was reported at the end of the prescription or after the prescription
Strunk (2008)[25]	No controller medication	Time to inadequate control after steroid step-down	No improvement in asthma control (futility analysis)
	FEV_1 < 50%pred		Recruitment was discontinued early (292 screened, only 55 randomized)
	>3 hospitalizations in past year		
	Sinus surgery in past year		
	Lung comorbidities		
Sutherland (2010)[26]	Exacerbation within 6 weeks	Asthma control	No differences in asthma control
	ARI within 6 weeks	Pulmonary function	No improvement
	>2 exacerbations or ARI prior to entry	Exhaled nitric oxide	No improvement
	Smoking	BHR	Improved
	History of smoking, ≥10 pack-years	Rescue medication use	No improvement
	Lung comorbidities	AQL	No improvement
Hahn (2012), current study	None	Overall asthma symptoms	Randomized: no improvements in any outcome
		AQL	Open label: improved overall asthma symptoms and AQL score at end of prescription that persisted after prescription (improvements maximal at the 9-month study point)
		ACQ	

*Other than for safety and logistics.
ACQ, asthma control questionnaire; ARI, acute respiratory illness; AQL, asthma quality of life; BHR, bronchial hyperresponsiveness; Cpn, *Chlamydia pneumoniae*; ECP, eosinophil cationic protein; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; Ig, immunoglobulin; IL, interleukin; LRTi, lower respiratory tract illness; Mpn, *Mycoplasma pneumoniae*; NNT, number needed to treat; PCR, polymerase chain reaction; PEF, peak expiratory flow.

allocated to placebo discontinued study medication because of side effects. Compared with placebo, subjects taking azithromycin (randomized and OL combined) reported significantly more nausea (33% vs 9% for placebo), stomach pain (42% vs 12% for placebo), and diarrhea (42% vs 15% for placebo). The majority of these side effects were mild to moderate in severity and no subject taking azithromycin (either randomized or OL) reported discontinuation because of side effects. There were no significant differences in side effect frequency or severity when the arm randomized to azithromycin was compared with the cohort that elected OL azithromycin (Table 4).

Discussion

We found no significant treatment effect for subjects randomized to azithromycin. Our a priori power calculations were based on overall asthma symptom results from a previous pilot study that did not experience self-exclusion of patients with severe asthma, and in this study we were unable to demonstrate any statistically significant effects of

treatment on overall asthma symptoms. We found a 15% difference in AQL score of ≥1-unit improvement favoring azithromycin (NNT = 7) at 12 months that was not statistically significant (Table 3). Because a change in AQL score ≥1 represents an important clinical improvement, we advocate future azithromycin effectiveness trials of patients with mild to moderate asthma that are adequately powered to detect, at a minimum, an NNT of 10 to 20 for this chronic, morbid, and expensive condition.

The participants in the OL cohort had more severe asthma than those randomized to azithromycin, and their asthma was often refractory to guideline treatment. The OL cohort demonstrated statistically and clinically significant benefits that largely persisted at 12 months compared with placebo treatment. Six months after completing azithromycin, the OL cohort experienced a 21% improvement in overall asthma symptoms, a 1.8-unit (26%) improvement in AQL score and a 1.2-unit (20%) improvement in asthma control score. This AQL score change was more than 3 times greater than the minimal clinically important change (0.5 units) and exceeded the threshold (1.5 units) for a large change.[14] These azithromycin treatment benefits are greater and of longer duration than those achieved by current guideline treatments. For example, a recent efficacy trial in nonsmoking adults with uncontrolled asthma achieved lower benefits (1) when inhaled steroid dose was doubled (0.05 AQL questionnaire units, 0.03 asthma control units); (2) when the long-acting bronchodilator salmeterol was added (0.28 AQL questionnaire units, 0.31 asthma control units); or (3) when tiotropium was prescribed (0.15 AQL questionnaire units, 0.22 asthma control units).[15] In AZMATICS, treating only 2 OL subjects with azithromycin was required to achieve an AQL score improvement of 1 unit or greater in one of them (NNT = 2) at 9 months. Because 80% of asthma morbidity and health care utilization is experienced by patients with the most severe forms of the disease,[16] our results suggest that azithromycin therapy may be a promising novel intervention to decrease the burden of morbidity and cost associated with management of severe and uncontrolled adult asthma, and future blinded, randomized trials are warranted.

Previous Studies

Ten randomized controlled trials of second-generation macrolides/azalides (azithromycin, clarithromycin, and roxithromycin) for chronic stable asthma have been published (see Tables 5 and 6 for more details).[17–26] A 2005 Cochrane review concluded that there was insufficient evidence to confirm or refute the role of macrolide treatment in chronic asthma.[1] Since 2005, 3 additional trials of macrolides in chronic adult asthma have reported patient-oriented outcomes.[22,24,26] Hahn et al[22] (our pilot) performed a practice-based effectiveness trial that included mainly patients with mild to moderate asthma who were randomized to 6 weekly doses of azithromycin or placebo. Outcomes of interest included asthma symptoms, AQL, and levels of *C. pneumoniae*–specific antibodies up to 3 months after the completion of treatment. Azithromycin treatment had a significant effect on asthma symptom reduction during the treatment phase, which persisted through study termination 3 months later. Elevated levels of *C. pneumoniae*–specific immunoglobulin A antibodies predicted worsening of asthma symptoms.[22] AQL improved by 0.25 units, but the change was not statistically significant. Simpson et al[24] performed an efficacy trial in nonsmoking adults with severe refractory asthma who were randomized to 8 weeks of clarithromycin or placebo and were followed for an additional 4 weeks after treatment. Clarithromycin treatment significantly improved AQL at the end of treatment (median AQL questionnaire score at baseline, 5.5; median score at end of treatment, 6.2; $P = .01$). The improvement was more pronounced in subjects with "noneosinophilic" ("neutrophilic") asthma and waned 4 weeks after treatment.[24] Sutherland et al[26] performed an efficacy study that included bronchoscopic polymerase chain reaction (PCR) testing for *C. pneumoniae* and *M. pneumoniae* in a highly selected group of mild to moderate asthmatics who were randomized to 16 weeks of clarithromycin or placebo without observation after treatment. Clarithromycin treatment did not improve overall asthma control at the end of treatment. The PCR-positive subgroup had weak evidence ($P = .06$) of a more rapid achievement in asthma control score ≥0.5 units (the minimal important clinical difference). This study excluded subjects older than 60 years, those with severe asthma, smokers, those with coexisting chronic obstructive pulmonary disease (COPD), and any pa-

tient with more than 2 exacerbations or respiratory tract infections before study entry (http://www.clinicaltrials.gov/ct/show/NCT00318708?order = 2). Each of these exclusion characteristics is associated with biomarkers of *C. pneumoniae* infection.[27–31] These exclusions probably explain the detection of fewer atypical pathogens than anticipated (13% PCR positive compared with an expected 50%).[26] AZMATICS included at least 53 asthma subjects (55%) who would have been excluded from typical asthma efficacy trials such as that of Sutherland et al[26]; 15% of AZMATICS subjects were aged 60 years or older; 24% had severe persistent asthma; 11% were current smokers; 25% had a history of 10 or more pack-years of cigarette use; and 15% had coexisting COPD.

AZMATICS' OL results are consistent with Simpson et al[24] for subjects with severe asthma in that they demonstrate a significant benefit after macrolide treatment and are unique among all studies of macrolide treatment for asthma (see Tables 5 and 6) in that they demonstrate persistent benefits 1 year after treatment. Outcomes of the AZMATICS study also support findings of Hahn et al[22] and Sutherland et al,[26] who reported lesser or no benefit associated with macrolide treatment in subjects with mild to moderate asthma. However, all 3 studies were underpowered to detect clinically significant effects in milder asthma.

Treatment, Side Effects, and Serious Adverse Events

We chose azithromycin over other macrolides, including clarithromycin, because it has (1) unique pharmacodynamic properties that allow weekly dosing to maintain high intracellular drug levels, (2) few drug interactions, and (3) a good safety profile that has been demonstrated in more than 5000 adults in previous trials.[32,33] A recent trial of daily azithromycin for 1 year in patients with COPD actually found a lower incidence of macrolide-resistant oral pathogens in the azithromycin-treated arm compared with the placebo arm, alleviating concerns about antibiotic resistance.[34,35] An additional benefit is that, unlike clarithromycin, azithromycin has no residual taste that might compromise blinding in some subjects. The cumulative azithromycin doses in the randomized and OL arms (8400 mg vs 9750 mg, respectively) differed somewhat, but both treatment regimens resulted in equally effective and prolonged intracellular concentrations of azithromycin.[36] Side effects were generally mild and of similar frequency for both doses (Table 4), and no serious adverse events or discontinuations because of side effects were attributed to either azithromycin regimen.

Mechanism of Action

Our trial did not directly address mechanism of action. AZMATICS was designed to distinguish between effects that wane (consistent with direct anti-inflammatory mechanisms) or persist (consistent with antimicrobial mechanisms) after completion of treatment. We interpret the residual benefits found in OL subjects to be most consistent with an antimicrobial mechanism of action.

Limitations

This trial has several limitations, including the absence of biomarkers for atypical infections and follow-up pulmonary function testing (PFT). Lack of PFT precluded the comparison of objective measures of airway function with the patient-oriented clinical outcomes and decreased our sample size by excluding enrollment of otherwise-eligible patients (Figure 1). Importantly, AZMATICS was underpowered to detect clinically important improvements in subjects with mild to moderate persistent asthma. Our sample was limited to subjects with Internet access, was deficient in minority representation, and did not standardize asthma treatment across groups.

Our proportion lost to follow-up exceeded 20% at year 1, which lowered the quality of our trial from a level 1 to a level 2 study, according to the Strength of Recommendation Taxonomy, a standard adopted by many primary care publications.[37] The placebo control group (with milder asthma) and the OL cohort (with more severe asthma) did not have comparable asthma prognoses. Because asthma prognosis is generally worse for severe asthma, this disparity could have diminished contrasts (ie, tendency to bias the OL results toward a null effect). By necessity, the OL cohort subjects were not blinded to azithromycin allocation. If placebo effects are accepted as an explanation only during the time period of medication administration, then placebo effects cannot be invoked as an explanation for peak benefits that occurred 6 months after completing azithromycin treatment. It is possible that other mechanisms, such as denial, cognitive dissonance, or both, could have promoted

systematic misreporting by OL subjects. A true treatment effect is supported by the strength and consistency of the results (including 2 validated instruments, the AQL questionnaire and the asthma control questionnaire), by agreement with our blinded pilot results[22] and by the results of the principal investigator's (DLH) previous prospective observational cohort study that included patients with confirmed *C. pneumoniae* infections.[38] Although exploratory analyses suggest that smoking may have a significant modifying effect, AZMATICS was underpowered for subgroup analyses. Future studies should be powered for robust subgroup analyses, which can be performed only if the subgroups are enrolled rather than systematically excluded from enrollment.

The Importance of Effectiveness Studies of Asthma

A technology assessment commissioned by the National Asthma Education Panel states that "short-term drug efficacy studies are over-represented in the present literature."[39] Standard exclusion criteria in adult asthma efficacy trials include restricted age ranges, pulmonary function parameters, current and previous smoking, and lung comorbidities such as coexisting COPD.[4,5] As a result, 95% of asthma subjects have been systematically excluded from the trials used to support guideline recommendations.[4,5] Thus, asthma efficacy trials and the guidelines derived from them may not generalize well to the broader population of asthma sufferers.

To address some of the limitations of asthma efficacy studies, AZMATICS was designed as a "pragmatic" or "practical clinical trial" to include a diverse population of study participants, recruitment of participants from different practice settings, and a range of health outcomes.[40,41] We enrolled subjects from community-based practices and applied exclusion criteria that were solely based on safety and logistic considerations (eg, the ability to complete the study). Furthermore, AZMATICS is, to our knowledge, the first trial to include an OL arm for subjects with severe asthma who otherwise would have been excluded based on patient preference. Using this approach, we succeeded in enrolling 1 of 3 screened patients; we probably would have been able to enroll closer to 1 in 2 screened patients had funding to perform PFT been available (Figure 1). Our actual enrollment (30%) and potential enrollment (50%) experience exceeds the 5% enrollment average for asthma efficacy trials.[5] Future larger pragmatic trials may achieve even higher enrollment proportions by using physician-diagnosed asthma as the primary eligibility criterion and using PFTs as a baseline covariate and an outcome measure but not as an additional eligibility criterion.

Conclusions

This randomized trial of 12 weekly doses of azithromycin failed to demonstrate statistically significant improvements after 1 year in any of the patient-oriented outcomes that we evaluated. Interpretation is complicated because a significant number of eligible asthma subjects—who had greater than average severity of the disease—declined to be randomized. Azithromycin treatment was well tolerated overall, and in the OL group with more severe, often refractory asthma, there seemed to be persisting substantive, clinically significant benefits to asthma symptoms, AQL, and asthma control for at least 6 months in about half of treated subjects. We advocate further effectiveness trials of persistent asthma of all severity categories that include an array of biomarkers to allow for secondary subgroup analyses, the results of which might favor one biological mechanism over another. However, at this time we do not favor approaches that insist on making a microbiologic diagnosis before randomization[26] or treatment,[42] as advocated by others, because this approach inevitably excludes patients who are unable to undergo or tolerate bronchoscopy. Future cost-effectiveness studies may help to determine whether making a microbiologic diagnosis via bronchoscopy versus treatment of all severe refractory asthma patients (especially given the NNT suggested by this study) is the more cost-effective approach.

Pending further randomized trials and given the relative safety of azithromycin and the significant disease burden from severe refractory asthma, prescribing prolonged azithromycin therapy to patients with uncontrolled asthma may be considered by managing clinicians, particularly for patients who have failed to respond to conventional treatment and as an alternative to instituting immunomodulatory agents.

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