CHEST

Effect of Azithromycin on Asthma Remission in Adults With Persistent Uncontrolled Asthma

A Secondary Analysis of a Randomized, Double-Anonymized, Placebo-Controlled Trial

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BACKGROUND: Asthma remission is a potential treatment goal.

RESEARCH QUESTION: Does adding azithromycin to standard therapy in patients with persistent uncontrolled asthma induce remission compared with placebo?

STUDY DESIGN AND METHODS: This secondary analysis used data from the Asthma and Macrolides: the Azithromycin Efficacy and Safety (AMAZES) clinical trial—a double-anonymized placebo-controlled trial that evaluated the safety and efficacy of azithromycin on asthma exacerbations. The primary remission definition (referred to as clinical remission) was zero exacerbations and zero oral corticosteroids during the previous 6 months evaluated at 12 months and a 5-item Asthma Control Questionnaire score $\leq$ 1 at 12 months. Secondary remission definitions included clinical remission plus lung function criteria (postbronchodilator $FEV_1 \geq 80\%$ or postbronchodilator $FEV_1 \leq 5\%$ decline from baseline) and complete remission (sputum eosinophil count $<$ 3% plus the aforementioned criteria). Sensitivity analyses explored the robustness of primary and secondary remission definitions. The predictors of clinical remission were identified.

RESULTS: A total of 335 participants (41.5% male; median age, 61.01 years; quartile 1-3, 51.03-68.73) who completed the 12-month treatment period were included in the analysis. Twelve months of treatment with azithromycin induced asthma remission in a subgroup of patients, and a significantly higher proportion in the azithromycin arm achieved both clinical remission (50.6% vs 38.9%; $P = .032$) and clinical remission plus lung function criteria (50.8% vs 37.1%; $P = .029$) compared with placebo, respectively. In addition, a higher proportion of the azithromycin group achieved complete remission (23% vs 13.7%; $P = .058$). Sensitivity analyses supported these findings. Baseline factors (eg, better asthma-related quality of life, absence of oral corticosteroid burst in the previous year) predicted the odds of achieving clinical remission. Azithromycin induced remission in both eosinophilic and noneosinophilic asthma.

INTERPRETATION: In this study, adults with persistent symptomatic asthma achieved a higher remission rate when treated with azithromycin. Remission on treatment may be an achievable treatment target in moderate/severe asthma, and future studies should consider remission as an outcome measure.

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KEY WORDS: asthma; azithromycin; remission

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Take-home Points

Study Question: Does adding azithromycin to standard therapy in patients with persistent uncontrolled asthma induce clinical remission compared with placebo?

Results: Over one-half of the study population treated with azithromycin achieved clinical remission, and the remission rate was significantly higher in the azithromycin arm than the placebo arm.

Interpretation: Clinical remission was shown to be possible in a significant proportion of people with persistent symptomatic asthma treated with azithromycin.

Asthma is a common chronic respiratory condition affecting > 300 million people worldwide, leading to a significant health and economic burden.[1] The etiology and pathobiology of asthma are complex and usually represent a multitude of interactions between various levels of the host biome (ie, genes to cells to tissues to organs) and environmental factors (eg, allergens, microbes, pollutants).[2] This heterogeneity makes asthma a difficult-to-treat disease in some patients.

Over the past decade, greater awareness of the underlying pathophysiology of asthma (eg, disentangling the inflammatory subtypes such as T helper 2 (Th2) high, Th2 low, and allergic inflammatory pathways) has led to the development of new add-on therapies such as biologics (eg, omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab) acting on various effector molecules of the Th2/allergic inflammatory cascade.[3] Biologics are an efficacious tailored treatment approach for Th2 high asthma with the potential to deliver a high level of asthma control and exacerbation reduction, but are not effective in Th2 low asthma. Conversely, macrolide antibiotics have been extensively investigated for treating obstructive airway diseases (eg, asthma, COPD, bronchiectasis).[4-7] A robust randomized controlled trial (RCT) and a subsequent individual participant data meta-analysis of three RCTs concluded that long-term azithromycin is effective in managing persistent uncontrolled asthma, including both Th2 high and Th2 low asthma.[4,8] Consequently, many clinical practice guidelines now recommend long-term macrolide antibiotics (eg, azithromycin) in the management of severe asthma as an add-on therapy.[9-12]

These novel treatment approaches reduced the overall burden experienced by people with asthma and, to some extent, modified the disease progression. However, achieving asthma remission has been given less attention until recently.[3,13,14] As more and better therapies become available, the treatment goals for asthma are in transition, and research suggests that it may be feasible to aim for remission.[3,13,15] Achieving asthma remission involves attaining a high level of disease control and eliminating exacerbations for a prolonged period with or without ongoing treatment. Previous studies also considered whether optimization or stabilization of lung function and resolution of underlying pathology are part of remission criteria in asthma.[16-24] This is an emerging area, and various definitions of remission have been proposed with varying degrees of rigor in criteria. Currently, there is a call for a consensus definition for asthma remission.[3,25,26]

Studies have evaluated the potential of biologics in achieving asthma remission.[16-24,27,28] However, to our knowledge, no studies have yet evaluated the efficacy of

ABBREVIATIONS: ACQ-5 = 5-item Asthma Control Questionnaire; AMAZES = Asthma and Macrolides: the Azithromycin Efficacy and Safety; AQLQ = Asthma Quality of Life Questionnaire; OCS = oral corticosteroid; RCT = randomized controlled trial; Th2 = T helper 2

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a macrolide antibiotic to achieve remission. In this post hoc analysis, we evaluated the efficacy of long-term azithromycin in achieving remission in patients with persistent uncontrolled asthma.

Study Design and Methods

This study represents a secondary analysis of the Asthma and Macrolides: the Azithromycin Efficacy and Safety (AMAZES) clinical trial data—a randomized, double-anonymized, placebo-controlled clinical trial that evaluated the effect of azithromycin on asthma exacerbations in adults with persistent uncontrolled asthma.[4] Eligible patients were recruited between June 2009 and January 2015 from eight Australian sites. The detailed methodology, patient eligibility, and primary outcome data are published elsewhere.[4] In brief, adults with symptomatic asthma despite current use of inhaled corticosteroid and long-acting bronchodilator and without hearing impairment or abnormal QT interval were recruited. Treatment group participants received 500 mg azithromycin three times a week for 48 weeks as add-on therapy, and the control group participants received matching placebo. Participants were followed up for 12 months at regular intervals. The AMAZES clinical trial was registered on the Australian and New Zealand Clinical Trials registry (No. ACTRN12609000197235).

The trial was approved by institutional ethics committees of all participating hospitals, and all patients provided written informed consent prior to enrollment.

Outcome Measures

The outcome measures were predefined in the statistical analysis plan.

The primary remission definition, referred to as clinical remission, included the following three components: (1) zero exacerbations (no oral corticosteroid [OCS] burst or hospitalization or ED visit due to asthma); (2) zero OCS use (ie, absence of both OCS burst and maintenance OCS) both assessed during the previous 6 months at 12-month follow-up; and (3) 5-item Asthma Control Questionnaire (ACQ-5) score $\leq$ 1 at 12 months. Secondary remission definitions included clinical remission plus optimization or stabilization of lung function at 12 months (optimization of lung function was defined as postbronchodilator $FEV_1 \geq 80\%$ predicted, and stabilization of lung function was defined as a change in postbronchodilator FEV_1 not greater than a 5% decline from the baseline) and complete remission defined as sputum eosinophil count < 3% plus the aforementioned criteria.

Additional sensitivity analyses explored the following: (1) a stringent ACQ-5 cutoff of 0.75 at 12 months; (2) ACQ-5 score $\leq$ 1 at multiple time points (ie, 6 and 12 months); and (3) clinical remission plus lung function criterion, which allows a maximum of 10% FEV_1 decline from baseline.

In subgroup analyses, we determined the proportion of participants who achieved clinical remission in people with different airway inflammation subcategories such as eosinophilic (sputum eosinophil count > 3% and neutrophil level < 61%), neutrophilic (sputum neutrophil level > 61% and eosinophil count < 3%), and paucigranulocytic (sputum eosinophil count < 3% and neutrophil level < 61%).[4]

Statistical Analysis

Statistical analyses were performed using Stata 14.2 (StataCorp); results are reported as mean $\pm$ SD for normally distributed data and median (quartiles 1 and 3) for nonnormally distributed data. Proportions of participants meeting the composite outcome remission and individual remission criteria were reported descriptively. Each predefined remission definition was compared between treatment and placebo arms using the χ^2 test. Unadjusted logistic regression was used to quantify the intervention effect on various remission definitions.

The number needed to treat was calculated by inverting absolute risk reduction (risk difference) between two groups.[29]

The predictors of clinical remission were identified using the data from the treatment arm. Univariate analysis (χ^2 or Fisher exact test for categorical data and Student t test or Wilcoxon rank sum test for continuous data) was used initially to explore the predictors. The variables with $P \leq .20$ in the univariate analysis were entered in the multivariate model. A backward selection of the variables was used, with an exclusion criterion of $P > .20$. The removal of variables was completed one at a time. The revised model was compared with the previous level using the likelihood ratio test, checking for an improvement in fit. The same number of participants was used in the model each time, allowing for valid comparison with the full model via the likelihood ratio test. The goodness of fit of the final model was confirmed by the Hosmer-Lemeshow test. Results were considered statistically significant when $P < .05$.

Results

A total of 335 participants (azithromycin: n = 168; placebo: n = 167) had final follow-up remission data and were included in this analysis (Fig 1). There was no difference between the baseline characteristics of those who were included in this analysis and those who were excluded from this analysis due to the unavailability of data. The baseline characteristics of the included participants are presented in Table 1. Participants had a median age of 61.0 years (quartile 1-3, 51.0-68.7), and 41.5% were male. Their median ACQ-5 score at baseline was 1.6 (quartile 1-3, 1.2-2.2), and mean FEV_1 % predicted postbronchodilator $\pm$ SD was 72.5 $\pm$ 19.4, with 53.9% who experienced an OCS burst in the previous year and 3.3% who were on maintenance OCS at baseline.

Remission Assessment

The proportions of participants achieving the predefined definitions of remission are presented in Table 2. The ORs and corresponding CIs are presented in Figure 2. A significantly higher proportion in the azithromycin arm achieved both clinical remission (50.6% vs 38.9%; $P = .032$) and clinical remission plus lung function criteria (50.8% vs 37.1%; $P = .029$) compared with placebo, respectively. In addition, a higher proportion of the

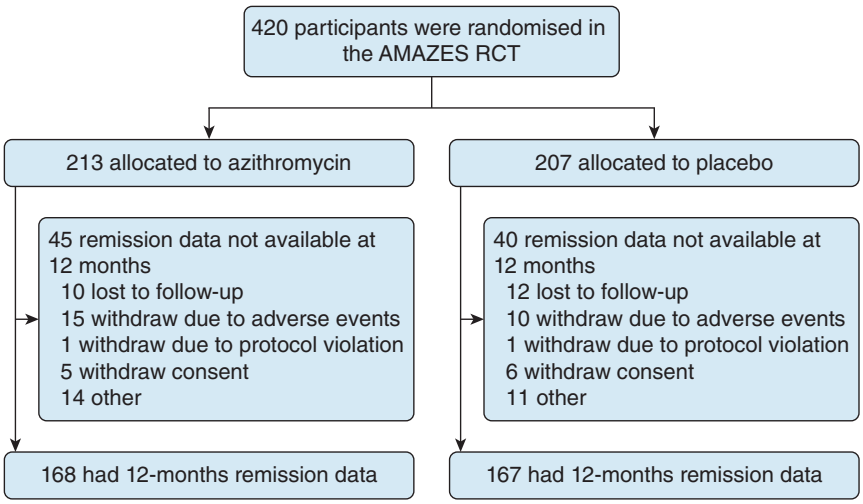

Figure 1 – *Trial profile. AMAZES = Asthma and Macrolides: the Azithromycin Efficacy and Safety; RCT = randomized controlled trial.*

azithromycin group achieved complete remission (23.0% vs 13.7%; $P = .058$).

Sensitivity Analyses: All sensitivity analyses conducted supported the primary and secondary analyses results (Table 2): (1) ACQ-5 cutoff of 0.75 at 12 months (38.7% vs 22.2%; $P = .001$); (2) ACQ-5 score ≤ 1 at multiple time points (39.9% vs 26.9%; $P = .012$); and (3) allowing FEV_1 10% decline from baseline (52.4% vs 38.7%; $P = .030$).

Subgroup Analyses: Approximately one-half of the population achieved clinical remission in all subcategories assessed, including eosinophilic (57%), neutrophilic (42%), and paucigranulocytic (50%) (Fig 3).

TABLE 1] Baseline Characteristics

Characteristic	Placebo (n= 167)	Azithromycin (n= 168)
Age, y	60.37 (49.79-68.71)	61.67 (51.88-68.73)
Male	70 (41.9)	69 (41.1)
BMI, kg/m^2	28.73 (25.43-33.11)	29.67 (25.90-33.61)
Smoking status		
Does not smoke	104 (62.3)	106 (63.1)
Previously smoked	63 (37.7)	62 (36.9)
Asthma duration, y	33.44 (14.88-50.10)	32.86 (19.04-48.79)
OCS burst in the past year[a]	89 (53.6)	91 (54.2)
Hospitalization in the past year	19 (11.4)	22 (13.1)
ED visit in the past year	25 (15.0)	27 (16.1)
Unscheduled GP visit for asthma in the past year	87 (52.1)	93 (55.4)
FEV_1 % predicted pre-BD, mean (SD)	72.35 (19.79)	71.56 (20.76)
FVC % predicted pre-BD, mean (SD)	82.76 (16.02)	82.85 (15.18)
FEV_1/FVC pre-BD, mean (SD)	67.24 (11.59)	66.26 (12.00)
FEV_1 % predicted post-BD, mean (SD)	73.36 (19.29)	71.67 (19.63)
FVC % predicted post-BD, mean (SD)	83.07 (15.09)	83.04 (14.58)
FEV_1/FVC post-BD, mean (SD)	68.03 (11.96)	65.99 (12.75)
ACQ-5 mean	1.60 (1.20-2.20)	1.60 (1.20-2.20)
AQLQ, mean	5.16 (4.53-5.78)	5.19 (4.53-5.84)
mOCS	5 (3.0)	6 (3.6)

Data are presented as median (quartile 1-3) or No. (%), unless otherwise indicated. ACQ-5 = 5-item Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; BD = bronchodilator; GP = general practitioner; mOCS = maintenance OCS; OCS = oral corticosteroid.
[a]Missing values: n = 1.

TABLE 2] Remission Analysis

	Remission Criteria	Placebo		Azithromycin		*P* Value
		No.[a]	No. (%)[b]	No.[a]	No. (%)[b]	
1	ACQ-5 score ≤ 1 at 12 mo	167	87 (52.1)	168	103 (61.3)	.089
2	No exacerbations in the last 6 mo	167	116 (69.5)	168	134 (79.8)	.030
3	No maintenance OCS use in last 6 mo	167	162 (97.0)	168	163 (97.0)	.99
	Clinical remission	167	65 (38.9)	168	85 (50.6)	**.032**
4	Postbronchodilator FEV_1 ≥ 80% or ≤ 5% decline from baseline	124	109 (87.9)	126	109 (86.5)	.74
	Clinical remission plus lung function criteria	124	46 (37.1)	126	64 (50.8)	**.029**
5	Sputum eosinophil count < 3%	167	74 (44.3)	168	72 (42.9)	.79
	Complete remission	124	17 (13.7)	126	29 (23.0)	.058
Sensitivity analysis						
1	Clinical remission using ACQ-5 cutoff of 0.75 at 12 mo	167	37 (22.2)	168	65 (38.7)	**.001**
2	Clinical remission evaluating ACQ-5 at multiple time points (ie, ACQ-5 score ≤ 1 at 6 and 12 mo)	167	45 (26.9)	168	67 (39.9)	**.012**
3	Clinical remission + lung function criteria (post-BD FEV_1 ≥ 80% predicted or ≤ 10% decline from baseline)	124	48 (38.7)	126	66 (52.4)	**.030**

ACQ-5 = 5-item Asthma Control Questionnaire; BD = bronchodilator; OCS = oral corticosteroid. Bold indicates statistical significance.
[a]Total observations available.
[b]Proportions are based on the available observations.

Number Needed to Treat: Nine patients had to be treated with azithromycin to have one additional patient achieve clinical remission compared with placebo.

Predictors of Achieving Clinical Remission

After the univariate analysis (e-Table 1), six variables (BMI, OCS burst, unscheduled general practitioner visit due to asthma exacerbations, prebronchodilator FEV_1 % predicted, ACQ-5 mean, and Asthma Quality of Life Questionnaire [AQLQ] mean) were entered in the multivariable model. Of those, two variables (OCS burst and AQLQ mean) were retained in the model (Table 3). Each unit increase in baseline AQLQ mean, which equated to a clinically significant improvement in asthma quality of life, increased the chance of achieving remission by 2.2 times. Likewise, those who required an OCS burst for asthma in the previous year before study entry had 62% less chance of achieving remission. The Hosmer-Lemeshow test indicated a good model fit, and there was no collinearity in the final model. The model correctly classified 68.1% of remission cases.

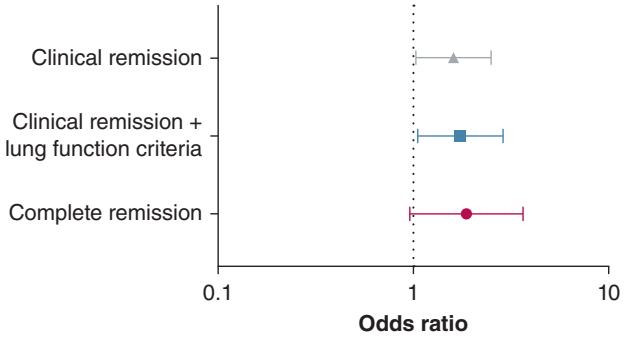

Figure 2 – *Placebo vs azithromycin: the odds of achieving various categories of remission (ORs and 95% CIs are displayed). The scale of the x axis is log10.*

Discussion

This post hoc analysis was conducted to determine the proportion of people with asthma who had inhaled corticosteroid/long-acting beta-agonist treatment-resistant asthma treated with long-term azithromycin who achieved asthma remission and to compare the remission rate between treatment and placebo groups. The analysis was performed by applying various predefined composite definitions of asthma remission to

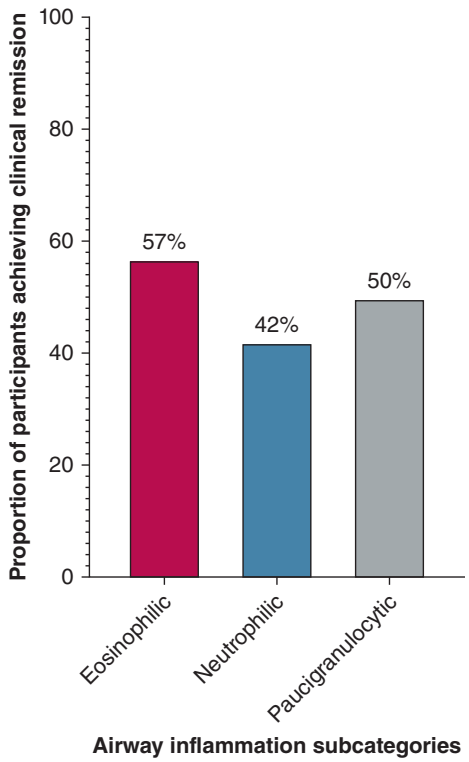

Figure 3 – *Proportion achieving clinical remission in eosinophilic, neutrophilic, and paucigranulocytic subcategories of airway inflammation.*

the AMAZES clinical trial cohort. Over one-half of the study population treated with azithromycin achieved clinical remission and clinical remission plus lung function criteria. The remission rate was consistently higher in the azithromycin arm than the placebo arm. All primary, secondary, and sensitivity analyses favored the treatment arm. These results demonstrate that on-treatment clinical remission is a realistic goal for those who are treated with long-term azithromycin.

To our knowledge, this is the first study to evaluate the efficacy of a macrolide antibiotic to induce asthma remission in patients with moderate to severe asthma. Also, this is the first study to demonstrate that remission can be achieved in noneosinophilic asthma in which no other promising treatment options are currently available; however, an inhibitor of thymic stromal lymphopoietin, tezepelumab, has shown effectiveness in both eosinophilic and noneosinophilic asthma.[30] It is promising that approximately one-half of the treated population achieved clinical remission in all subcategories assessed, including people with noneosinophilic asthma.

TABLE 3] Independent Predictors of Clinical Remission

Variable	OR	*P* Value	95% CI
OCS burst in the previous year	0.38	.006	0.19-0.76
AQLQ mean	2.21	< .001	1.5-3.26

AQLQ = Asthma Quality of Life Questionnaire; OCS = oral corticosteroid.

Several real-world studies[17-24,27,28] and post hoc analyses of clinical trials[16,31] have explored the efficacy of various biologics in inducing asthma remission. Most of these studies included patients with severe asthma, and one dupilumab study included patients with moderate to severe uncontrolled asthma.[32] The asthma remission rate in these studies ranged between 15% and 38%. In addition, a small outlier study reported a remission rate of 69%.[20] Participants in the current study achieved a comparatively higher remission rate, and this could be explained by the fact that the current cohort had a lower baseline disease severity, which is known to be associated with greater likelihood of achieving remission.[3] The studies used a broad range of remission definitions. Although all these studies included the absence of exacerbations and a high level of symptom control in the definition, the assessment criteria used were highly variable between studies. For example, some included the elimination of only severe exacerbations, whereas some included the elimination of all types of exacerbations. Likewise, the evaluation period (6 months, 12 months, etc), OCS measures (eg, point estimate of no maintenance OCS use just at the final follow-up time point [ie, not for a certain period], permitting maintenance OCS and eliminating only OCS burst, not allowing any types of OCS use [ie, no maintenance or burst use]), and assessment of symptom control (ACQ-5 score $\leq$ 0.75, ACQ-5 score $\leq$ 1, ACQ-5 score $\leq$ 1.5, Asthma Control Test score $\geq$ 20, etc) were not identical. In addition, some included lung function criteria (some used optimization defined as achieving postbronchodilator $FEV_1 \geq 80\%$ predicted, some used stabilization defined as no decline of lung function from baseline, and some used certain degree of improvement from baseline) and biomarkers (eg, blood eosinophil count) in the definition. Consequently, the remission rate may not be comparable between these studies and the current study. This highlights the importance of having a uniform definition of asthma remission when assessing the efficacy of various treatments in achieving remission.

Such innovations have already been initiated. The American College of Allergy, Asthma, and Immunology; American Academy of Allergy, Asthma, and Immunology; and American Thoracic Society expert

panel proposed a six-component definition for asthma remission.[26] The panel comprised a small group of experts (N = 11) and used a modified Delphi approach to reach a consensus. The proposed definition has not been evaluated using clinical data, and the authors acknowledged that the proposed framework is a starting point for future research, and that definitions are expected to change. It was not feasible to evaluate this proposed definition in the current analysis due to its retrospective nature and data unavailability.

In our analysis, we used a reasonably stringent clinical remission definition that included the absence of all types of exacerbations and OCS use during the remission period in addition to achieving an ACQ-5 score $\leq$ 1 at the end of treatment. We also assessed clinical remission plus lung function criteria using a composite lung function criterion (ie, optimization or stabilization of lung function to account for various factors such as the natural decline of lung function, daily variability, impact of bronchodilator use, and effect of factors such as age, smoking status, BMI, ethnicity, and menopausal status).[33-35] Optimization included all those who achieved normal lung function at the end of treatment (ie, postbronchodilator $FEV_1 \geq$ 80% predicted), and stabilization was defined as not more than 5% decline from baseline. We also conducted a sensitivity analysis which allowed a maximum decline of 10% from baseline.[33,36] Complete remission was additionally defined as sputum eosinophil count < 3%, a direct marker of underlying inflammation.[3] None of the previous studies used sputum eosinophil count in the remission definition, but a couple included indirect markers (eg, blood eosinophil count, fractional exhaled nitric oxide).[18,20] All these secondary outcomes and sensitivity analyses supported the primary analysis, indicating the robustness of study findings; however, complete remission just missed statistical significance.

It is also interesting to see that a significant proportion of patients in the placebo arm achieved remission. To be included in the AMAZES study, optimization of asthma treatment and $\geq$ 80% adherence during the 2-week run-in period was required. Patients should also be clinically stable with no recent exacerbations, infections, or changes in maintenance medication for at least 4 weeks before study entry. This initial intervention and close monitoring during the study might have led to a higher placebo effect. A previous placebo-controlled benralizumab RCT reported 25% remission in the placebo arm, defined as no OCS use, no exacerbations, and 6-item Asthma Control Questionnaire score < 1.5.[16] Another placebo-controlled dupilumab RCT reported 20% remission in the placebo arm, defined as no OCS use, no exacerbations, ACQ-5 score < 1.5, and either improvement in prebronchodilator $FEV_1 \geq$ 100 mL or postbronchodilator % predicted $FEV_1 \geq$ 80%.[31] Both of these studies included patients with Th2 high asthma, whereas the AMAZES study included both patients with Th2 high and low asthma. Moreover, as previously noted, the AMAZES cohort had a lower baseline disease severity, and the current analysis used a different remission definition. These differences also might have led to a higher remission rate among the AMAZES placebo cohort. Another noteworthy observation is that we used a more stringent cutoff for the ACQ-5 (ie, 0.75), and the difference in remission rate between placebo and azithromycin was higher, indicating the importance of carefully defining the cutoffs. This also might have some implications in the sample size requirement for a future clinical trial targeting remission.

In our study, we found that nine patients needed to be treated to get an additional outcome. This number-needed-to-treat is lower than previously reported for benralizumab[37]; however, this might be due to other variables as previously discussed. In the present study, regression analysis found that the absence of OCS burst in the year prior to study entry (an indicator of disease control) and baseline AQLQ score (an indicator of asthma symptom burden in daily life) were predictive of remission. These findings reiterate the association between baseline asthma control and clinical remission.

For people with asthma, exacerbations are a significant cause of morbidity and mortality and are associated with progressive loss of lung function and future adverse outcomes. Additionally, OCS is frequently used to treat exacerbations, which carries significant and irreversible risk to almost all organ systems of the body. Hence, achieving remission may have huge health and economic impact, and future asthma treatment should aim to achieve asthma remission. Biologics are parenteral dosage forms, cost-prohibitive in low- and middle-income countries, and restricted to specific populations in high-income countries, whereas azithromycin is a low-cost oral therapy recommended for the treatment of moderate to severe asthma.[9-12] However, concerns such as the potential for antimicrobial resistance and side-effects, including cardiac, sensory, and GI effects, may limit its widespread use. Future studies may also consider a longer-term follow-up because disease stabilization and relapse may

depend on the length of remission. It is also important to establish the impact of achieving asthma remission on underlying pathology (eg, bronchial hyperresponsiveness, smooth muscle thickness).

This analysis provides the first insight, to our knowledge, into the possibility of achieving asthma remission using long-term azithromycin and in noneosinophilic asthma. The data obtained from a robust RCT and the specific strengths and limitations of the RCT were published elsewhere.[4] The strength of the current analysis included using predefined definitions of asthma remission and sensitivity analyses evaluating various remission definitions with various degrees of rigor in criteria. These data can be constructively used to reach a consensus definition of asthma remission. The weakness includes the post hoc nature of the analysis inflating the type 1 error. The remission definition is still evolving, and the current components and the biomarker cutoffs are subject to change. Therefore, various possible definitions were used to further explore achievable targets for asthma remission. Also, some of the observed remissions in this study might be a natural phenomenon (regression toward the mean).

Interpretation

This study showed that clinical remission is possible in a subset of people with persistent symptomatic asthma treated with azithromycin. The positive trend observed in this study raises the hope of asthma remission as a realistic therapeutic goal.

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Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Additional information: The e-Table is available online under "Supplementary Data."

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