

ORIGINAL ARTICLE

Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level

S.C. Lazarus, J.A. Krishnan, T.S. King, J.E. Lang, K.V. Blake, R. Covar, N. Lugogo, S. Wenzel, V.M. Chinchilli, D.T. Mauger, A.-M. Dyer, H.A. Boushey, J.V. Fahy, P.G. Woodruff, L.B. Bacharier, M.D. Cabana, J.C. Cardet, M. Castro, J. Chmiel, L. Denlinger, E. DiMango, A.M. Fitzpatrick, D. Gentile, A. Hastie, F. Holguin, E. Israel, D. Jackson, M. Kraft, C. LaForce, R.F. Lemanske, Jr., F.D. Martinez, W. Moore, W.J. Morgan, J.N. Moy, R. Myers, S.P. Peters, W. Phipatanakul, J.A. Pongratic, L. Que, K. Ross, L. Smith, S.J. Szeffler, M.E. Wechsler, and C.A. Sorkness, for the National Heart, Lung, and Blood Institute AsthmaNet*

ABSTRACT

BACKGROUND

In many patients with mild, persistent asthma, the percentage of eosinophils in sputum is less than 2% (low eosinophil level). The appropriate treatment for these patients is unknown.

METHODS

In this 42-week, double-blind, crossover trial, we assigned 295 patients who were at least 12 years of age and who had mild, persistent asthma to receive mometasone (an inhaled glucocorticoid), tiotropium (a long-acting muscarinic antagonist), or placebo. The patients were categorized according to the sputum eosinophil level (<2% or ≥2%). The primary outcome was the response to mometasone as compared with placebo and to tiotropium as compared with placebo among patients with a low sputum eosinophil level who had a prespecified differential response to one of the trial agents. The response was determined according to a hierarchical composite outcome that incorporated treatment failure, asthma control days, and the forced expiratory volume in 1 second; a two-sided P value of less than 0.025 denoted statistical significance. A secondary outcome was a comparison of results in patients with a high sputum eosinophil level and those with a low level.

RESULTS

A total of 73% of the patients had a low eosinophil level; of these patients, 59% had a differential response to a trial agent. However, there was no significant difference in the response to mometasone or tiotropium, as compared with placebo. Among the patients with a low eosinophil level who had a differential treatment response, 57% (95% confidence interval [CI], 48 to 66) had a better response to mometasone, and 43% (95% CI, 34 to 52) had a better response to placebo (P=0.14). In contrast 60% (95% CI, 51 to 68) had a better response to tiotropium, whereas 40% (95% CI, 32 to 49) had a better response to placebo (P=0.029). Among patients with a high eosinophil level, the response to mometasone was significantly better than the response to placebo (74% vs. 26%) but the response to tiotropium was not (57% vs. 43%).

CONCLUSIONS

The majority of patients with mild, persistent asthma had a low sputum eosinophil level and had no significant difference in their response to either mometasone or tiotropium as compared with placebo. These data provide equipoise for a clinically directive trial to compare an inhaled glucocorticoid with other treatments in patients with a low eosinophil level. (Funded by the National Heart, Lung, and Blood Institute; SIENA ClinicalTrials.gov number, NCT02066298.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Lazarus at the Division of Pulmonary and Critical Care Medicine and the Cardiovascular Research Institute, University of California, San Francisco, M-1336, 505 Parnassus Ave., San Francisco, CA 94143, or at lazma@ucsf.edu.

*A complete list of the investigators in the National Heart, Lung, and Blood Institute AsthmaNet is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 19, 2019, at NEJM.org.

N Engl J Med 2019;380:2009-19.

DOI: 10.1056/NEJMoa1814917

Copyright © 2019 Massachusetts Medical Society.

ASTHMA IS HETEROGENEOUS, AND MANY patients do not have an acceptable response to currently available treatment, most of which targets eosinophilic inflammation. In previous studies, investigators found that approximately half of patients with asthma had a poor response to inhaled glucocorticoids¹⁻³ and that eosinophilic airway inflammation was not ubiquitous in the patients.⁴⁻⁷ In contrast to patients who have a percentage of sputum eosinophils of 2% or more, in whom the forced expiratory volume in 1 second (FEV₁) increases with the use of inhaled glucocorticoids, those with a low eosinophil level (<2%) may not have a response to glucocorticoids.⁷ Thus, the two subgroups of eosinophil levels may represent two different phenotypes of asthma with different needs for therapy.^{8,9}

Guidelines recommend the use of inhaled glucocorticoids in all patients with persistent asthma.^{10,11} Because in approximately 50% of patients, mild, persistent asthma may not be associated with sputum eosinophilia, it is important to determine prospectively whether these patients benefit from inhaled glucocorticoids and, if not, to consider alternative treatments. Since the risk of monotherapy with long-acting beta-agonists (LABAs)¹² ruled out their use, we considered tiotropium, a long-acting muscarinic antagonist (LAMA), as a safe alternative in a controller medication.¹³⁻¹⁶ Thus, in the Steroids in Eosinophil Negative Asthma (SIENA) trial, we compared an inhaled glucocorticoid (mometasone) and tiotropium with placebo in patients with mild, persistent asthma, according to the patients' sputum eosinophil level at baseline.

METHODS

PATIENTS

We enrolled patients who were at least 12 years of age and who had received a clinical diagnosis of asthma and met the guideline criteria of the National Asthma Education and Prevention Program for step 2 asthma treatment.^{10,11} The asthma diagnosis was confirmed by either an increase of 200 ml in the FEV₁ (and representing an increase of ≥12%) after the administration of albuterol or a 20% reduction in FEV₁ in response to a provocative concentration of inhaled methacholine (PC₂₀) of 16 mg per milliliter or less. Patients were excluded if they had received an inhaled

Figure 1 (facing page). Trial Design and Randomization.

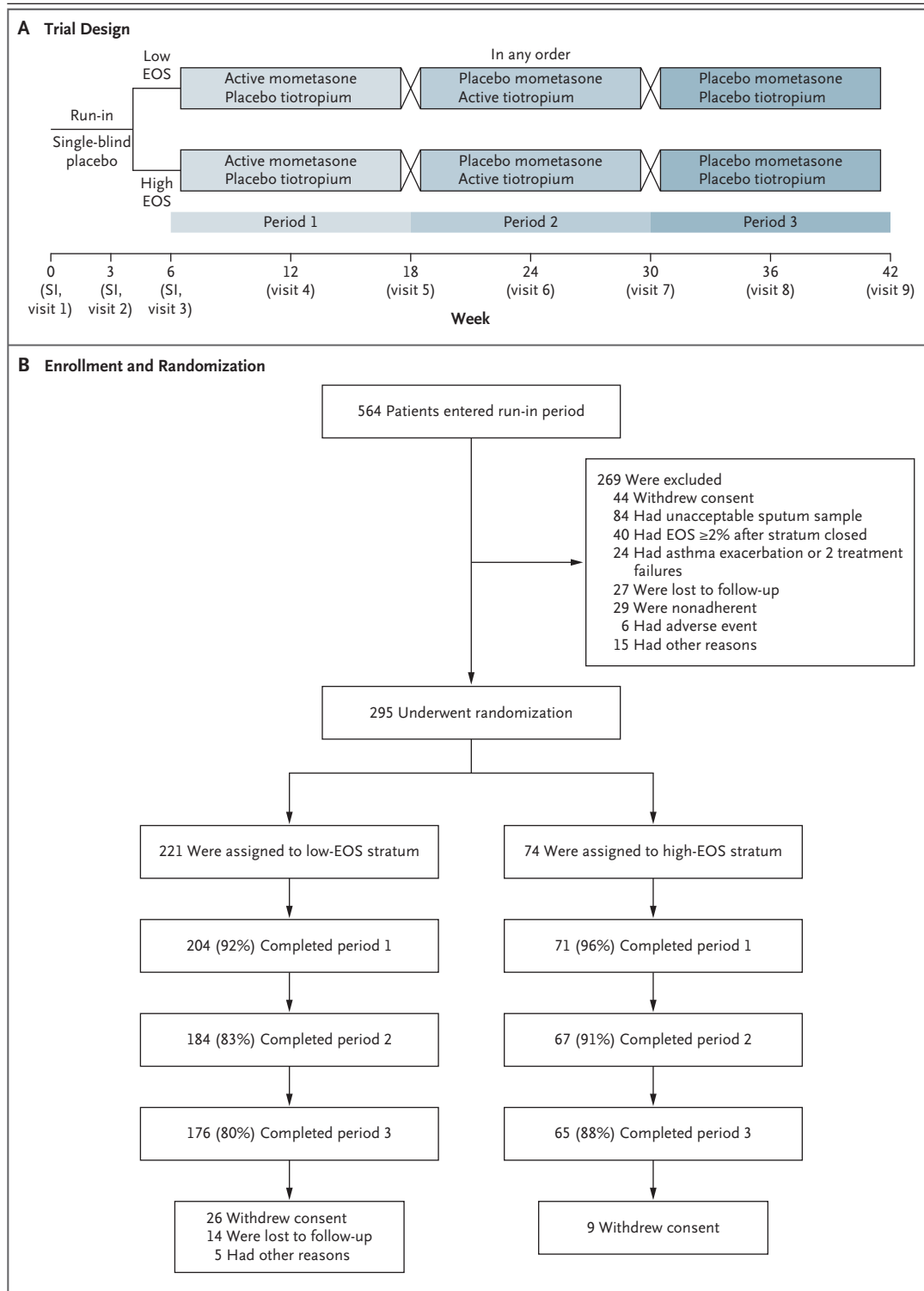
Panel A shows the trial design calling for the enrollment of patients who met the guideline criteria for step 2 asthma treatment in a 6-week single-blind placebo run-in period for characterization of asthma. Sputum induction (SI) was performed up to three times to guarantee the collection of two acceptable samples. At the end of the run-in period, patients who continued to meet the criteria for step 2 treatment and who met the adherence criteria for medication use and diary completion were stratified according to the sputum eosinophil (EOS) level (<2% or ≥2%) and were randomly assigned to receive one of three blinded regimens in random sequence for 12 weeks each. Throughout the trial, patients used an electronic diary to record asthma symptoms, nighttime awakenings, and morning and evening peak expiratory flow. Inhaler use was tracked by device dose counters. Panel B shows the number of patients who enrolled in the trial, underwent randomization, and completed the trial. A sputum sample was deemed to be unacceptable if it contained more than 80% squamous cells, if there was an inadequate sputum volume, or if the patient was unable to continue the induction procedure for at least 4 minutes. After 74 patients were categorized as being in the high-eosinophil stratum, subsequent patients with a high eosinophil level did not undergo randomization.

glucocorticoid within 3 weeks, an oral glucocorticoid within 6 weeks, or omalizumab within 3 months; had a respiratory infection within 4 weeks; had any cigarette use during the previous 12 months or a lifetime use of more than 10 pack-years; had a history of life-threatening asthma; or had an FEV₁ of less than 70% of the predicted value.

TRIAL DESIGN

We conducted this randomized, double-blind, placebo-controlled crossover trial at 24 sites in the United States that are included in the AsthmaNet consortium of the National Heart, Lung, and Blood Institute (NHLBI). The protocol, modifications, and statistical analysis plan are available with the full text of this article at NEJM.org. Adult patients provided written informed consent; for adolescents, parents or legal guardians provided written informed consent, and adolescents provided assent.

The patients were enrolled in a 6-week, single-blind placebo run-in period for characterization of their asthma, sputum eosinophilia, and asthma control and to establish adherence of more than 75% to the trial agent and daily completion of an electronic diary (Fig. 1A). Spirometric mea-



measurements were performed and albuterol reversibility was assessed at the first visit. If reversibility was not shown, the patients returned for

methacholine bronchoprovocation before the second visit. Sputum induction was performed up to three times during the run-in period to obtain

two acceptable samples for cell counts on the basis of a validated protocol.^{3,12,17,18}

The patients were classified as having a high eosinophil level if eosinophils made up at least 2% of at least one sputum sample. Patients with two sputum samples that contained less than 2% of eosinophils were designated as having a low eosinophil level. We obtained samples of serum periostin, blood eosinophils, and exhaled nitric oxide each time sputum induction was performed. The patients entered the double-blind crossover phase at the end of the run-in period if they continued to meet the criteria for step 2 treatment, had provided two acceptable sputum samples, met the adherence criteria for medication use and diary completion, did not have two or more episodes of treatment failure or one asthma exacerbation (Sections 4.1 and 4.2 in the Supplementary Appendix, available at NEJM.org), and the severity of asthma had not escalated to meet the criteria for step 3 treatment.

PROTOCOL REVISION

We anticipated that approximately 50% of the recruited patients would have a low eosinophil level.^{7,8} However, after 112 patients had undergone randomization, we found that 76% of these patients who first enrolled in the trial had a low eosinophil level. Thus, we revised the order of our trial objectives to focus the primary outcome on a comparison between an inhaled glucocorticoid and placebo and between a LAMA and placebo among the patients with a low eosinophil level. Comparisons of treatments in the high-eosinophil stratum and between the two eosinophil strata became secondary objectives and were included as an important positive control but not for outcome comparisons. This change in the priority of trial objectives occurred while all outcome data were masked and before the completion of enrollment and analysis of the trial results. The revision was approved by the steering committee, by the NHLBI, and by the NHLBI-appointed data and safety monitoring board.¹⁹

TRIAL REGIMENS

We assigned patients in the two eosinophil strata to a three-treatment, crossover trial for a total of 36 weeks of randomized treatment. During each 12-week period, the patients received twice-daily mometasone (at a dose of 220 μg with the Asmanex Twisthaler or 200 μg with the

Asmanex HFA [Merck]), once-daily tiotropium (at a dose of 5 μg with Spiriva Respimat [Boehringer Ingelheim]), or twice-daily placebo. (Details regarding the assignment of the inhaler device are provided in Section 6.1 in the Supplementary Appendix.) Trial-group assignments were masked by the use of matched masked inhalers that delivered placebo. To account for transitioning from one trial group to another, diary data from the initial 4 weeks of each 12-week treatment period were omitted from the analysis. Treatment failure and asthma exacerbations that occurred during this 4-week transition period were counted as events assigned to the ongoing trial agent.

EVALUATION INSTRUMENTS

All the patients used an electronic diary (Spirotel, Medical International Research) to record symptoms, medication use, nighttime awakenings, and morning and evening peak expiratory flow. The patients were seen every 6 weeks and assessed by phone at the 3-week point between visits. We used standard AsthmaNet procedures to assess asthma characteristics.^{20,21} In addition, we administered the Asthma Control Test (in which scores range from 5 [uncontrolled] to 25 [well controlled], with a minimally important difference of 3)²² and the Asthma Bother Profile (in which scores range from 0 [minimum effect] to 75 [maximum effect])²³ at every visit. During visits 3, 5, 7, and 9, we administered the Asthma Symptom Utility Index (which ranges from 0 [worse symptoms] to 1 [fewer symptoms], with a minimally important difference of 0.09),²⁴ the Asthma-Specific Work Productivity and Activities Impairment Questionnaire (with results expressed as an impairment percentage),²⁵ and the Sinonasal Questionnaire (which evaluates the frequency of nasal symptoms on a scale from 0 [never] to 3 [daily])²⁶ (Table S3 in the Supplementary Appendix).

SAFETY ASSESSMENTS

Safety criteria were defined to ensure that the patients whose asthma control worsened received additional treatment early, before the development of an exacerbation. Treatment failure was defined and addressed as described previously (Section 4.1 in the Supplementary Appendix).²⁷ Patients who met the criteria for treatment failure received an open-label, high-dose inhaled glucocorticoid (mometasone at a dose of 440 μg

twice daily for 10 days) in addition to the double-blind trial agent. When necessary, the treatment period was extended so that at least 3 weeks elapsed between treatment with a high-dose inhaled glucocorticoid and crossover to the next trial period or trial completion. Patients who had two or more treatment failures or an asthma exacerbation during one treatment period were crossed over to the next treatment period or completed their final visit.

OUTCOME MEASURES

The primary outcome was the response to mometasone as compared with placebo and to tiotropium as compared with placebo among patients with a low eosinophil level who had a prespecified differential response to a trial agent. The response was determined according to a hierarchical composite outcome of asthma control that incorporated treatment failure, annualized number of asthma control days (defined as the number of days without the rescue use of albuterol, the use of a concomitant asthma medication, symptoms, urgent care visits, or peak expiratory flow at <80% of the baseline value), and FEV₁ on the basis of prespecified threshold criteria. We assessed the differential response for the comparisons between both mometasone and tiotropium with placebo.

The patients were defined as having a differential response if no treatment failures occurred in one period and at least one failure occurred in another trial period, if the number of annualized asthma control days was at least 31 days higher than that in another trial period, or if the FEV₁ at the end of the period was at least 5% higher than that in another trial period. If one trial agent (either of the active drugs or placebo) was better than the other with respect to the threshold for treatment failure, we ignored the number of asthma control days and FEV₁. If there was no difference for treatment failure, and the threshold for the number of asthma control days was met, we ignored the FEV₁. If there was no difference with respect to either treatment failure or the number of asthma control days, we considered the FEV₁ in the analysis. A patient was considered to have no differential response with respect to a given comparison if none of the thresholds were met.

Although we used a combination of all three hierarchical measures as a composite primary

outcome, each individual measure was considered separately as a secondary outcome. The secondary outcomes and prespecified exploratory outcomes are described in Sections 5.1 and 5.2 in the Supplementary Appendix.

TRIAL OVERSIGHT

The trial was funded by the NHLBI and approved by the AsthmaNet steering committee, an NHLBI-appointed protocol review committee, and a data and safety monitoring board. Mometasone and mometasone placebo were donated by Merck, tiotropium and tiotropium placebo by Boehringer Ingelheim, and albuterol by Teva. These companies did not play a role in the design of the trial, in the collection or interpretation of the data, or in the preparation of the manuscript. Each of the companies received a copy of the manuscript at the time that it was submitted for publication.

The authors were responsible for the trial design, data collection, data interpretation and analysis, manuscript preparation, and decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data, for the accuracy of the analyses, and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

The primary research questions were whether an inhaled glucocorticoid (mometasone) or a LAMA (tiotropium) was superior to placebo among patients with a low eosinophil level who had a differential response. We determined that a sample of 262 patients in this stratum would provide a power of 90% at a two-sided significance of 0.025 (Bonferroni correction) to detect a difference in probabilities of 0.20 while allowing for a 15% withdrawal rate and a 30% rate of no differential response. With the approval of the data and safety monitoring board, we closed enrollment at 221 patients in the low-eosinophil stratum, which provided a power of just under 85%.¹⁹

To evaluate each null hypothesis, we applied two-sided, exact binomial tests at the 0.025 significance level to data from patients who had a differential response, according to the hierarchical composite outcome. To assess potential effects of the trial period and seasonal factors, we performed a sensitivity analysis by applying logistic-regression models to data from patients who had a differential response, with covariates to adjust for differences between trial periods,

seasons of enrollment, and delivery device for mometasone (dry powder vs. metered-dose inhaler) (see Section 6.1 in the Supplementary Appendix).

Prespecified secondary analyses with the primary hierarchical composite outcome included the same analysis performed with data from patients in the high-eosinophil stratum, a comparison between mometasone and tiotropium performed in the same manner as described for the comparison between placebo and mometasone or tiotropium, and an exploratory subgroup analysis to evaluate the coprimary research hypotheses in adults only. We created receiver-operating-characteristic (ROC) curves and estimated the area under the curve (AUC) to determine the predictive value of other biomarkers for sputum eosinophilia or response to treatment. We used linear mixed-effects models to analyze secondary outcome measures for questionnaires and diary data for longitudinal data after adjustment for baseline values, trial period, eosinophil stratum, and trial group within the eosinophil stratum, as well as a random effect for clinical site.

All analyses were performed on the intention-to-treat principle in which data were included for all the patients who had undergone randomization. Patients with missing data were conservatively assumed to have had a similar response to both mometasone and tiotropium, so these patients were imputed as not having had a differential response for the purpose of the intention-to-treat analysis with the use of single imputation. A tipping-point analysis was performed to evaluate the effect of various assumptions applied to patients with missing outcome data (see Section 6.2 in the Supplementary Appendix).

RESULTS

PATIENTS

The trial was conducted from July 2014 through March 2018. Of the 564 patients who were enrolled in the run-in period, two acceptable sputum samples were available for 366 patients. Of these samples, 268 (73%) were classified as having a low eosinophil level and 98 (27%) as having a high eosinophil level. Of the remaining patients, 109 provided one acceptable sputum sample, and 89 provided no acceptable samples. Of the 366 patients with two acceptable sputum

samples, 295 underwent randomization: 221 to the low-eosinophil subgroup and 74 to the high-eosinophil subgroup (Table 1 and Fig. 1B, and Tables S1 and S2 in the Supplementary Appendix).

A total of 58 patients (20%) were between the ages of 12 and 18 years; of these patients, 40 (69%) had a low eosinophil level. Among the 221 patients with a low eosinophil level, those who completed at least two trial periods and provided data for each comparison in the primary analysis included 176 (80%) for the comparison between mometasone and placebo and 181 (82%) for the comparison between tiotropium and placebo, which permitted the assessment of a differential response. Among the 74 patients with a high eosinophil level, 67 (91%) completed the analysis periods for the comparison between mometasone and placebo and 62 (84%) completed the periods for the comparison between tiotropium and placebo.

At the time of enrollment, all the patients had mild asthma (mean baseline FEV₁ before bronchodilation, 90 to 93% of the predicted value). During the 12 months before enrollment, 23% had had at least one urgent care visit for asthma and 19% had received an oral glucocorticoid for asthma.

ADHERENCE

There was no significant difference among the three trial groups in the rate of adherence to the blinded medications and to diary completion, as measured by the electronic devices used for this purpose. The rates did not vary according to eosinophil subgroup (Section 7.1 in the Supplementary Appendix).

DIFFERENTIAL RESPONSE TO TRIAL AGENTS

A differential response for the comparison between mometasone and placebo was observed in 130 of 221 patients (59%) with a low eosinophil level: 34% had better asthma control while receiving mometasone, 25% had better control while receiving placebo, 21% showed no between-group difference, and 20% with missing data were imputed as having no between-group difference. For the comparison between tiotropium and placebo, 36% had better control while receiving tiotropium, 24% had better control while receiving placebo, 22% showed no between-group difference, and 18% with missing data were imputed as having no between-group difference (Fig. 2A).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Low Eosinophil Level (N=221)	High Eosinophil Level (N=74)
Demographic features		
Age — yr	31.2±13.8	31.1±14.2
Male sex — no. (%)	76 (34)	35 (47)
Asthma history		
Median age at diagnosis (IQR) — yr	8.0 (3.0–15.0)	7.0 (3.0–14.0)
Duration of asthma — yr	19.2±10.9	20.0±12.2
One or more asthma episodes requiring emergency care or unscheduled office visit in previous yr — no. (%)	52 (24)	17 (23)
One or more courses of systemic glucocorticoids in previous yr — no. (%)	41 (19)	14 (19)
Clinical and spirometric features		
Body-mass index†	29.1±7.8	26.5±5.7
Predicted FEV ₁ — %	92.7±12.4	89.5±10.8
Ratio of FEV ₁ to FVC	0.77±0.08	0.75±0.08
Geometric mean PC ₂₀ (±CV) — mg/ml‡	2.42±1.28	1.24±1.27
Bronchodilator response (4 puffs) — % change	9.6±7.1	12.7±8.5
Median fraction of exhaled nitric oxide (IQR) — ppb	21.5 (14.0–35.5)	55.5 (35.0–81.0)
Median blood eosinophil level (IQR) — %	2.6 (1.1–4.0)	4.8 (3.9–7.0)
Median periostin level (IQR) — ng/ml	51.7 (43.3–63.6)	56.3 (49.3–75.2)
Median score on Asthma Control Test (IQR)§	21.0 (20.0–23.0)	21.0 (19.0–23.0)
Patients with eczema or atopic dermatitis — no. (%)	67 (30)	27 (36)
Patients with ≥1 positive allergen test — no./total no. (%)	172/216 (80)	70/72 (97)

* Plus-minus values are means ±SD unless otherwise noted. CV denotes coefficient of variation, FEV₁ forced expiratory volume in 1 second, FVC forced vital capacity, and IQR interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ PC₂₀ denotes the provocative concentration of inhaled methacholine that results in a 20% reduction in the FEV₁.

§ The score on the Asthma Control Test ranges from 5 (uncontrolled) to 25 (well controlled), with a minimally important difference of 3.

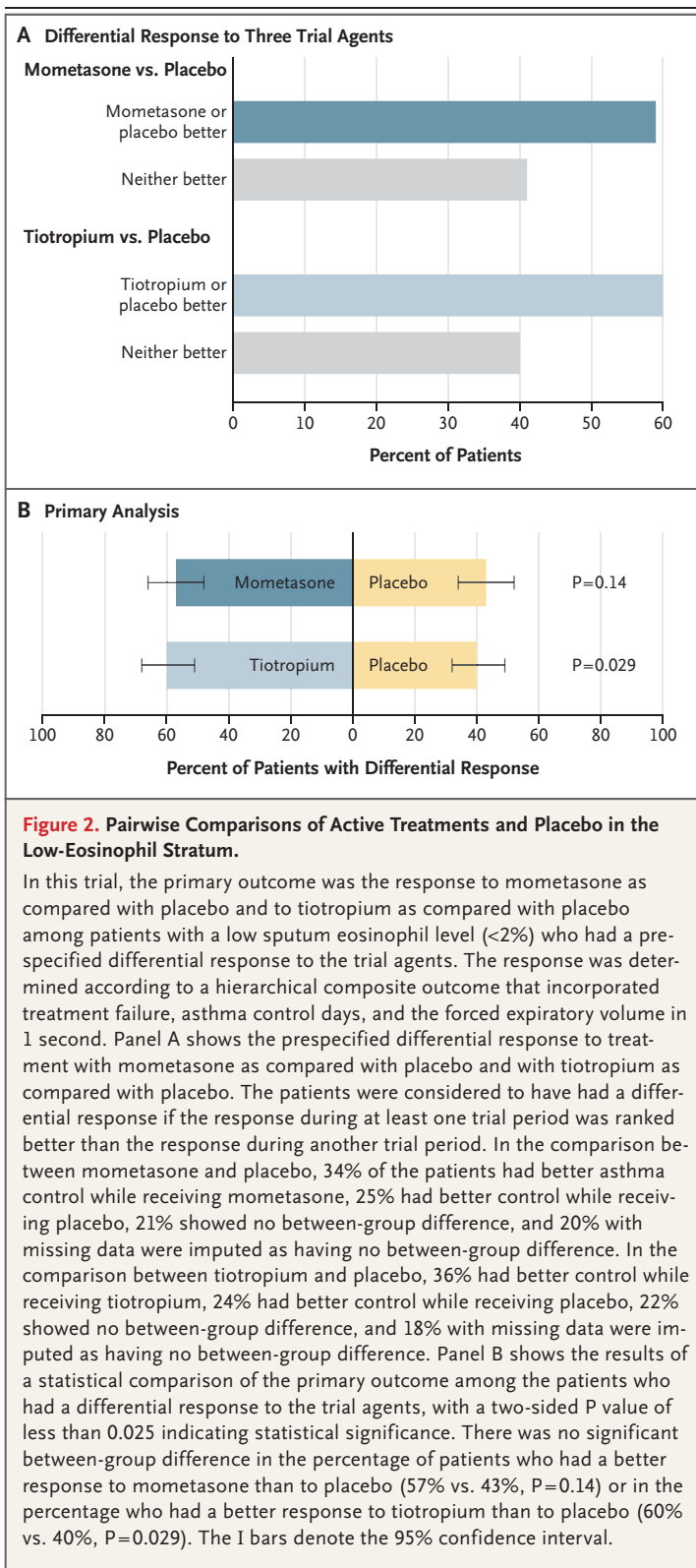
PRIMARY ANALYSIS

Among the patients with a low eosinophil level who had a differential response, there was no significant difference between the percentage who had a better response to mometasone (57%; 95% confidence interval [CI], 48 to 66) and those who had a better response to placebo (43%; 95% CI, 34 to 52; $P=0.14$); there was also no significant difference in the percentage who had a better response to tiotropium (60%; 95% CI, 51 to 68) and those who had a better response to placebo (40%; 95% CI, 32 to 49; $P=0.029$) (Fig. 2B). These conclusions did not change with sensitivity analyses that included adjustment for differences in the trial period, season of enrollment, and mometasone delivery device. However, our conclusions were not robust to assumptions

regarding missing data, since the results for the comparison between tiotropium and placebo would have been different under the missing-at-random assumption. Although the results of the comparison between mometasone and placebo were the same under the missing-at-random assumption, a tipping-point analysis showed that the results changed if we assumed that patients with missing data were twice as likely to have had a better response to mometasone than to placebo (Section 6.2 in the Supplementary Appendix).

SECONDARY ANALYSES

Among the patients with a high eosinophil level who had a differential response, 74% (95% CI, 60 to 86) had a better response to mometasone



and 26% (95% CI, 14 to 40) had a better response to placebo; the corresponding better responses were 57% (95% CI, 41 to 72) to tiotropium and 43% (95% CI, 28 to 59) to placebo (Fig. S1 in the Supplementary Appendix). The responses among the patients in the two eosinophil strata regarding the individual components of the hierarchical composite outcome are shown in Figures S2 and S3 in the Supplementary Appendix. In the two strata, the composite outcome was driven by increases in the FEV₁. Among the patients who had a differential response and who had a better response to mometasone than to tiotropium, there was no significant difference between the low-eosinophil stratum (48% vs. 52%) and the high-eosinophil stratum (55% vs. 45%) (Fig. S4 in the Supplementary Appendix).

EXPLORATORY ANALYSES IN ADULTS

Among adults in the low-eosinophil stratum who had a differential response, 59% (95% CI, 49 to 69) had a better response to mometasone and 41% (95% CI, 31 to 51) had a better response to placebo; the corresponding percentages were 62% (95% CI, 52 to 71) for tiotropium and 38% (95% CI, 29 to 48) for placebo. Among adults in the high-eosinophil stratum who had a differential response, 78% (95% CI, 62 to 90) had a better response to mometasone and 22% (95% CI, 10 to 38) had a better response to placebo; the corresponding percentages were 54% (95% CI, 37 to 71) for tiotropium and 46% (95% CI, 29 to 63) for placebo (Fig. S5 in the Supplementary Appendix).

We examined blood eosinophil levels and the fraction of exhaled nitric oxide as surrogates for the sputum eosinophil level by performing the two measurements whenever sputum samples were obtained. ROC curves showed that the blood eosinophil level was a “fair” predictor of a sputum eosinophil level of less than 2% and the fraction of exhaled nitric oxide was a “good” predictor,²⁸ with AUCs of 0.77 and 0.80, respectively. The blood eosinophil level and the fraction of exhaled nitric oxide each predicted response to mometasone (AUC, 0.63) but not to tiotropium (AUC, 0.48 and 0.54, respectively) (Figs. S6 through S8 in the Supplementary Appendix).

OTHER MEASURES OF CONTROL

In the patients with a high eosinophil level, scores on the Asthma Control Test and Asthma Symptom Utility Index were better among those who received mometasone than among those who received either tiotropium or placebo. The results for these and other secondary and exploratory outcomes — including findings on questionnaires, peak expiratory flow, and nocturnal awakenings — are listed in Table S3 in the Supplementary Appendix.

ADVERSE EVENTS

There were few adverse events, asthma exacerbations, or treatment failures among the patients. There was no significant difference in adverse events between the high-eosinophil stratum and the low-eosinophil stratum or between the two active treatment groups (Tables S4 and S5 in the Supplementary Appendix).

DISCUSSION

Several key findings emerged from our trial of mometasone and tiotropium involving patients with mild, persistent asthma who were stratified according to sputum eosinophil level. Nearly three quarters of the patients who underwent screening (and who represented broad geographic and economic distribution within the United States) were identified as having a low eosinophil level, a percentage that is much greater than has been reported in this population previously.⁷

Although the patients had mild asthma, they had sufficient symptoms (on >2 days per week, >2 nights per month, or albuterol rescue on >2 days per week) to meet the criteria for step 2 treatment (a daily inhaled glucocorticoid), according to the guidelines of the National Asthma Education and Prevention Program. A substantial percentage of these patients were at risk for a loss of asthma control. Sputum eosinophilia has been shown to predict the response to glucocorticoid therapy,^{6,7,29} and patients with a low sputum eosinophil level or a low level of type 2 airway inflammation do not have a favorable response to glucocorticoids.^{7,9} This finding suggests that standard treatment with mometasone may not be effective in this population, and we examined that hypothesis prospectively in this trial.

The trial was designed to examine two primary comparisons among the patients in the low-eosinophil stratum: the differential response to mometasone and to tiotropium, as compared with placebo, for three measures of asthma control that incorporated treatment failure, asthma control days, and FEV₁, with the use of prespecified threshold criteria. Nearly 60% of the patients in the low-eosinophil stratum had a differential response to one of the three trial agents, but the percentage who had a better response to either active drug was not significantly greater than the percentage who had a better response to placebo. In contrast, in a secondary analysis in the high-eosinophil stratum, the response to mometasone was clearly superior to the response to placebo.

We enrolled adolescents together with adults because the treatment guidelines include adolescents in their recommendations. However, we prespecified separate exploratory analyses in the adult group and the adolescent group. When we reanalyzed the primary outcomes among the adults in the low-eosinophil stratum, a larger percentage had a better response to tiotropium than to placebo. Among the 58 patients in the adolescent group, 40 (69%) had a low eosinophil level. However, the numbers of adolescent patients in the two eosinophil strata are too small to allow for meaningful statistical comparisons.

The use of inhaled glucocorticoids is recommended for nearly all patients with persistent asthma according to the belief that airway inflammation is ubiquitous in asthma and, if untreated, leads to airway remodeling.^{30,31} However, remodeling is far less common than once thought, and patients with a low level of type 2 airway inflammation do not have a favorable response to inhaled glucocorticoids. Our results extend these observations to a relatively large group of well-characterized patients with mild asthma who have a persistent sputum eosinophil level of less than 2%. In our trial, sputum eosinophilia was assigned on the basis of two induced sputum samples obtained approximately 3 weeks apart, rather than after a single determination, to minimize the potential of misclassification owing to variability over time.

Our results raise the question of whether treatment guidelines should be reevaluated for

patients with mild, persistent asthma for whom evidence of type 2 inflammation is lacking. Among such patients, adherence to prescribed regimens is often lacking because they tend to stop using inhaled glucocorticoids when they feel well, they have concern about potential adverse effects, or they perceive that the treatment is ineffective. Although our data for patients in the low-eosinophil stratum do not support current treatment recommendations, the appropriate controller treatment for these patients remains to be determined.

In our trial, 73% of the patients with mild, persistent asthma who underwent screening had a sputum eosinophil level of less than 2%; in 67% of these patients, the response to placebo was either as good as or better than the response to mometasone (Fig. S9 in the Supplementary Appendix). The need for a change in treatment strategy is further highlighted by a growing body of literature suggesting that mild, persistent asthma can be managed safely without the daily use of inhaled glucocorticoids and

by data showing that patients with a low eosinophil level may not have a favorable response to inhaled glucocorticoids. Among patients with a low eosinophil level, the daily use of inhaled glucocorticoids may increase the risk of side effects and the costs of maintenance treatment, with minimal clinical benefit. Our findings provide clinical equipoise for a larger and longer study to compare inhaled glucocorticoids with other treatments for the large number of patients with mild or moderate asthma. Biomarkers that have been used to guide treatment mainly in severe or refractory asthma^{1-7,9,32,33} may provide valuable direction in future trials to identify patients who are most likely to have a response to inhaled glucocorticoids or to an alternative therapy.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Supported by the National Heart, Lung, and Blood Institute. Tiotropium and tiotropium placebo were provided by Boehringer Ingelheim. Mometasone and mometasone placebo were provided by Merck. Albuterol was provided by Teva.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Stephen C. Lazarus, M.D., Jerry A. Krishnan, M.D., Ph.D., Tonya S. King, Ph.D., Jason E. Lang, M.D., Kathryn V. Blake, Pharm.D., Ronina Covar, M.D., Njira Lugogo, M.D., Sally Wenzel, M.D., Vernon M. Chinchilli, Ph.D., David T. Mauger, Ph.D., Anne-Marie Dyer, M.S., Homer A. Boushey, M.D., John V. Fahy, M.D., Prescott G. Woodruff, M.D., Leonard B. Bacharier, M.D., Michael D. Cabana, M.D., Juan C. Cardet, M.D., Mario Castro, M.D., James Chmiel, M.D., Loren Denlinger, M.D., Ph.D., Emily DiMango, M.D., Anne M. Fitzpatrick, Ph.D., Deborah Gentile, M.D., Annette Hastie, Ph.D., Fernando Holguin, M.D., Elliot Israel, M.D., Daniel Jackson, M.D., Monica Kraft, M.D., Craig LaForce, M.D., Robert F. Lemanske, Jr., M.D., Fernando D. Martinez, M.D., Wendy Moore, M.D., Wayne J. Morgan, M.D., James N. Moy, M.D., Ross Myers, M.D., Stephen P. Peters, M.D., Ph.D., Wanda Phipatanakul, M.D., Jacqueline A. Pongracic, M.D., Loretta Que, M.D., Kristie Ross, M.D., Lewis Smith, M.D., Stanley J. Szefer, M.D., Michael E. Wechsler, M.D., and Christine A. Sorkness, Pharm.D.

The authors' affiliations are as follows: the Division of Pulmonary and Critical Care Medicine and the Cardiovascular Research Institute (S.C.L., H.A.B., J.V.F., P.G.W.) and the Department of Pediatrics, Epidemiology, and Biostatistics (M.D.C.), University of California, San Francisco, San Francisco; the University of Illinois at Chicago (J.A.K.), the Department of Pediatrics, Rush University Medical Center (J.N.M.), Ann and Robert Lurie Children's Hospital of Chicago (J.A.P.), and Northwestern University, Feinberg School of Medicine (L.S.) — all in Chicago; the Department of Public Health Sciences, Penn State University, Hershey (T.S.K., V.M.C., D.T.M., A.-M.D.), and the University of Pittsburgh Asthma Institute (S.W., F.H.) and Allegheny General Hospital (D.G.), Pittsburgh — all in Pennsylvania; Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando (J.E.L., K.V.B.), and Nemours Children's Health System, Jacksonville (J.E.L., K.V.B.) — both in Florida; the Department of Pediatrics and Medicine, National Jewish Health, Denver (R.C., S.J.S., M.E.W.), and Children's Hospital Colorado, Aurora (R.C., S.J.S., M.E.W.) — both in Colorado; Duke Allergy, Asthma, and Airway Center, Duke University School of Medicine, Durham (N.L., M.K., L.Q.), Wake Forest University School of Medicine, Winston-Salem (A.H., W.M., S.P.P.), and North Carolina Clinical Research, Raleigh (C.L.) — all in North Carolina; the Departments of Pediatrics and Medicine, Washington University in St. Louis School of Medicine, St. Louis (L.B.B., M.C.); Brigham and Women's Hospital and Harvard Medical School (J.C.C., E.L.) and Boston Children's Hospital (W.P.) — all in Boston; Rainbow Babies and Children's Hospital, Cleveland (J.C., R.M., K.R.); the University of Wisconsin, Madison (L.D., D.J., R.F.L., C.A.S.); Columbia University, New York (E.D.); the Department of Pediatrics, Emory University, Atlanta (A.M.F.); and the Arizona Respiratory Center, University of Arizona, Tucson (F.D.M., W.J.M.).

REFERENCES

- Martin RJ, Szefer SJ, Chinchilli VM, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. *Am J Respir Crit Care Med* 2002;165:1377-83.
- Martin RJ, Szefer SJ, King TS, et al. The Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial. *J Allergy Clin Immunol* 2007;119:73-80.
- Deykin A, Lazarus SC, Fahy JV, et al. Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. *J Allergy Clin Immunol* 2005;115:720-7.
- Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology* 2006;11:54-61.
- Haldar P, Pavord ID. Noneosinophilic asthma: a distinct clinical and pathologic phenotype. *J Allergy Clin Immunol* 2007;119:1043-52.
- Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet* 1999;353:2213-4.
- McGrath KW, Icitovic N, Boushey HA,

- et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *Am J Respir Crit Care Med* 2012;185:612-9.
8. Woodruff PG, Boushey HA, Dolganov GM, et al. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci U S A* 2007;104:15858-63.
 9. Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009;180:388-95.
 10. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma — summary report 2007. *J Allergy Clin Immunol* 2007;120:Suppl:S94-S138.
 11. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
 12. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting β_2 -agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583-93.
 13. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26.
 14. Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol* 2011;128:315-22.
 15. Iwamoto H, Yokoyama A, Shiota N, et al. Tiotropium bromide is effective for severe asthma with noneosinophilic phenotype. *Eur Respir J* 2008;31:1379-80.
 16. Kerstjens HAM, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;367:1198-207.
 17. Fahy JV, Liu J, Wong H, Boushey HA. Analysis of cellular and biochemical constituents of induced sputum after allergen challenge: a method for studying allergic airway inflammation. *J Allergy Clin Immunol* 1994;93:1031-9.
 18. Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012;308:987-97.
 19. Sorkness CA, King TS, Dyer AM, et al. Adapting clinical trial design to maintain meaningful outcomes during a multicenter asthma trial in the precision medicine era. *Contemp Clin Trials* 2019;77:98-103.
 20. Jackson DJ, Bacharier LB, Mauger DT, et al. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. *N Engl J Med* 2018;378:891-901.
 21. Castro M, King TS, Kunselman SJ, et al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. *JAMA* 2014;311:2083-91.
 22. Schatz M, Kosinski M, Yaras AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol* 2009;124(4):719-23.e1.
 23. Hyland ME, Ley A, Fisher DW, Woodward V. Measurement of psychological distress in asthma and asthma management programmes. *Br J Clin Psychol* 1995;34:601-11.
 24. Bime C, Wei CY, Holbrook JT, Sockrider MM, Revicki DA, Wise RA. Asthma Symptom Utility Index: reliability, validity, responsiveness, and the minimal important difference in adult asthmatic patients. *J Allergy Clin Immunol* 2012;130:1078-84.
 25. Andreasson ESK, Berggren F. The validity of the Work Productivity and Activity Impairment questionnaire for patients with asthma (WPAI-Asthma): results from a Web-based study. *Value Health* 2003;6:780. abstract.
 26. Dixon AE, Sugar EA, Zinreich SJ, et al. Criteria to screen for chronic sinonasal disease. *Chest* 2009;136:1324-32.
 27. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.
 28. Tape TG. Interpreting diagnostic tests: the area under an ROC curve. Omaha: University of Nebraska Medical Center (<http://gim.unmc.edu/dxtests/>).
 29. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
 30. Haahtela T, Järvinen M, Kava T, et al. Comparison of a β_2 -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
 31. Haahtela T, Järvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
 32. Szeffler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115:233-42.
 33. Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138(6):1608-1618.e12.

Copyright © 2019 Massachusetts Medical Society.