

ORIGINAL ARTICLE

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

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ABSTRACT

BACKGROUND

Eosinophilic inflammation, which may be a consequence of interleukin-5 action, is a characteristic feature of some forms of asthma. However, in three previous clinical trials involving patients with asthma, blockade of this cytokine did not result in a significant improvement in outcomes. We studied the prednisone-sparing effect of mepolizumab, a monoclonal antibody against interleukin-5, in a rare subgroup of patients who have sputum eosinophilia and airway symptoms despite continued treatment with prednisone. Secondary objectives were to examine its effect on the number of eosinophils in sputum and blood, symptoms, and airflow limitation.

METHODS

In this randomized, double-blind, parallel-group trial involving patients with persistent sputum eosinophilia and symptoms despite prednisone treatment, we assigned 9 patients to receive mepolizumab (administered in five monthly infusions of 750 mg each) and 11 patients to receive placebo.

RESULTS

There were 12 asthma exacerbations in 10 patients who received placebo, 9 of whom had sputum eosinophilia at the time of exacerbation. In comparison, only one patient who received mepolizumab had an asthma exacerbation, and this episode was not associated with sputum eosinophilia ($P=0.002$). Patients who received mepolizumab were able to reduce their prednisone dose by a mean (\pm SD) of $83.8\pm 33.4\%$ of their maximum possible dose, as compared with $47.7\pm 40.5\%$ in the placebo group ($P=0.04$). The use of mepolizumab was associated with a significant decrease in the number of sputum and blood eosinophils. Improvements in eosinophil numbers, asthma control, and forced expiratory volume in 1 second were maintained for 8 weeks after the last infusion. There were no serious adverse events.

CONCLUSIONS

Mepolizumab reduced the number of blood and sputum eosinophils and allowed prednisone sparing in patients who had asthma with sputum eosinophilia despite prednisone treatment. (ClinicalTrials.gov number, NCT00292877.)

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MONOCLONAL ANTIBODIES AGAINST interleukin-5, a potent eosinophilic cytokine and growth factor, have not shown efficacy in three clinical trials¹⁻³ in patients with asthma, despite the effectiveness of this treatment in reducing the number of eosinophils in the airway and blood. This finding has raised questions about the role of eosinophils in the pathophysiology of asthma.

We reasoned that eosinophils may be in the pathobiologic chain of causation in a rare subgroup of patients with asthma who have persistent sputum eosinophilia despite treatment with oral prednisone. To test this hypothesis, we examined the prednisone-sparing effect of mepolizumab by assessing clinical exacerbations, the number of eosinophils in sputum and blood, symptoms, and forced expiratory volume in 1 second (FEV₁) as outcome variables during a programmed reduction in the dose of prednisone in patients with this unusual asthma phenotype.

METHODS

PATIENTS

From January 2005 through July 2007, 20 adult patients with asthma who required treatment with oral prednisone to control symptoms and still had persistent sputum eosinophilia were recruited from the clinics of the Firestone Institute for Respiratory Health (Table 1). These patients constituted less than 3% of the 800 adult patients with severe asthma in our practice. In all but two of the patients, more than 3% of cells in an induced sputum sample were identified as eosinophils, despite daily treatment for at least 4 weeks with prednisone (at a dose of 5 to 25 mg) and an inhaled corticosteroid at a high dose (equivalent to 600 to 2000 μ g of fluticasone). Two of the patients were included in the study in error and were therefore excluded from some but not all of the analyses before the randomization code was broken.

Within the previous 8 years, all patients had had evidence of asthma (i.e., variable airflow obstruction). All of them had at least a 25% reduction in FEV₁ at the time of exacerbations; 18 patients had an increase in FEV₁ of 200 ml (15%) after inhaling 200 μ g of albuterol. Two patients had airway hyperresponsiveness to methacholine; the provocative concentration of methacholine required to cause a 20% decrease in FEV₁ (PC₂₀) was 4 mg per milliliter (Table 1 in the Supple-

mentary Appendix, available with the full text of this article at NEJM.org). None of the patients were current smokers, and none were exposed to relevant seasonal allergens during the study. None of the patients had had an onset of asthma symptoms before the age of 6 years.

STUDY DESIGN

The study was a randomized, placebo-controlled, double-blind, parallel-group trial lasting up to 26 weeks. Patients were seen every 2 weeks and were randomly assigned to treatment at week 2. The treatment with a humanized monoclonal interleukin-5 antibody, mepolizumab (at a dose of 750 mg) or an identical placebo (normal saline diluent) was given intravenously over a 30-minute period at weeks 2, 6, 10, 14, and 18. Computer-generated randomization codes stratified patients into two groups of 10 according to the daily dose of prednisone they were receiving at the time of enrollment (<10 mg or \geq 10 mg). Within each of the two groups, patients were equally divided among those receiving mepolizumab and those receiving placebo. When either group was filled, no additional patients were recruited for that group. This process was designed to ensure that there would be equal numbers of patients in each severity stratum in the mepolizumab group and the placebo group.

Randomization codes were held by the pharmacy department, whose members were unaware of clinical details in the study groups. However, a pharmacy error resulted in 9 patients incorrectly receiving mepolizumab and 11 patients incorrectly receiving placebo.

The study had three phases (Fig. 1). In phase 1, we evaluated the effect of one infusion of a study drug at 4 weeks. In phase 2, we evaluated the reduction in the dose of prednisone after two infusions of a study drug. The dose of prednisone was reduced by 5 mg at weeks 6, 10, 14, 18, and 22, according to a predefined schedule if the patient had not had a defined exacerbation. In patients who had required a daily dose of 10 mg or more of prednisone at the time of enrollment, we reduced the daily dose to 2.5 mg rather than zero because of concern regarding the effects of total withdrawal. The reduction in the dose of prednisone was expressed as a percentage of the target reduction. In phase 3 (washout phase), we followed patients for 8 weeks after the last infusion of a study drug.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Mepolizumab (N=9)	Placebo (N=11)
Age (yr)	56.4±10.9	58.2±7.1
Male sex (no. of patients)	4	8
Height (cm)	166.2±14.5	168.6±9.9
Weight (kg)	85.8±16.7	89.5±14.9
Duration of symptoms (yr)	13.3±10.3	12.5±9.5
FEV ₁		
Previous minimum†		
Value (liters)	1.4±0.6	1.6±0.5
% of predicted value	48±17	52±13
Previous maximum†		
Improvement with bronchodilation (%)	28.4±12.03	24.6±10.6
Decrease during exacerbation (%)	42.0±16.9	45.5±13.7
Current postbronchodilation		
% of predicted value	66.6±18.3	74.3±17.9
Ratio of FEV ₁ to vital capacity (%)	63.8±16.2	65.9±13.1
Sputum eosinophils (%)		
Median	16.6	4.0
Range	1.6–54.3	0–35.3
Prednisone (mg/day)		
Median	10.0	10.0
Range	5.0–25.0	2.5–20.0
Duration of daily use of prednisone (yr)	9.3±7.6	8.9±8.5
Inhaled corticosteroids (µg/day)‡		
Median	1000	1000
Range	600–2000	1000–2000
Short-acting β-agonist (no. of puffs/wk)	10±6	9±8
Long-acting β-agonist (no. of patients)	9	9
Leukotriene-receptor antagonists (no. of patients)	2	1
Atopy (no. of patients)	3	4
Nasal polyp (no. of patients)	3	5
Smoking history of >10 pack-years (no. of patients)	2	3

* Plus–minus values are means ±SD. Values are those recorded at the time of screening unless otherwise stated. There were no significant differences between the two groups for any of the variables except the number of sputum eosinophils (P=0.03). FEV₁ denotes forced expiratory volume in 1 second.

† Previous lowest and highest values for FEV₁ refer to the historic lowest and highest values recorded since the patients were first seen in clinic. The individual values from which the means are derived and the duration of follow-up are provided in Table 1 in the Supplementary Appendix.

‡ The dose of inhaled corticosteroids is the equivalent of inhaled fluticasone.

The academic investigators designed the protocol with the aid of an employee of GlaxoSmithKline. The data were gathered, analyzed, and interpreted by the academic investigators, who also wrote the article. GlaxoSmithKline provided the mepolizumab but had no further role in the con-

duct of the study; in the collection, tabulation, analysis, and interpretation of data; or in any stage of the manuscript preparation.

The study was approved by the hospital's research ethics board. All patients provided written informed consent.

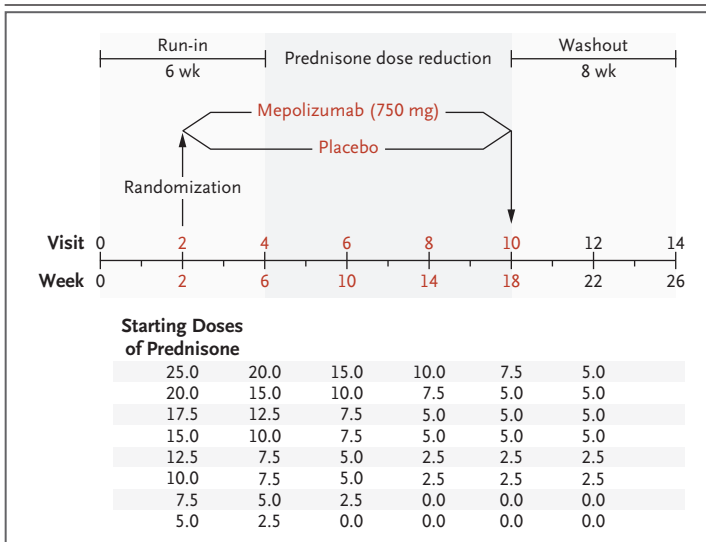


Figure 1. Protocol for Reduction in the Dose of Prednisone.

Infusions of either mepolizumab or placebo were administered at weeks 2, 6, 10, 14, and 18. After a 6-week run-in period, the dose of prednisone was then reduced at weeks 6, 10, 14, 18, and 22, according to a predefined schedule, if the patient had not had an exacerbation with an increase in the number of sputum eosinophils. Among the 20 patients in the study, there were eight different starting doses of prednisone. The doses were reduced according to the schedule that is shown. In patients who were receiving a daily dose of 10 mg or more of prednisone at baseline, the dose of the drug was not reduced to zero because of concern regarding withdrawal effects.

PRIMARY AND SECONDARY OUTCOMES

The primary outcomes of the study were the proportion of patients with exacerbations in each study group and the mean reduction in the dose of prednisone as a percentage of the maximum possible reduction, according to the protocol used in phase 2 of the study. Other variables that were measured at entry and every 2 weeks were results on the Juniper Asthma Control Questionnaire⁴ (with scores ranging from 0 to 6 and higher scores indicating worse asthma control; the minimal clinically important change in the score is 0.5) and on a Likert scale⁵ (with scores ranging from 7 to 35, and lower scores indicating greater severity of symptoms; the minimal clinically important change in the score is 0.5 for each symptom, for a total of 2.5), maximal curves of expiratory flow volume to measure FEV₁ and slow vital capacity 15 minutes after the administration of 200 μg of albuterol, and quantitative counts of sputum cells and blood eosinophils. In addition, we measured the PC₂₀ (if the FEV₁ was >70% of the predicted value) and blood samples for levels of electrolytes, urea, creatinine, and alanine and as-

partate aminotransferases at study entry. The blood tests were repeated at week 26.

Secondary outcomes were a reduction in the number of eosinophils in sputum and blood in phase 1; the time to an exacerbation, a reduction in the number of sputum and blood eosinophils, and changes in FEV₁ and symptom scores in phase 2; and a reduction in the number of sputum and blood eosinophils and changes in FEV₁ and symptoms in phase 3.

EXACERBATIONS

Exacerbations were defined as either a patient-initiated increase in the daily dose of albuterol of four or more puffs to control symptoms of chest tightness or as any one of the following: nocturnal or waking respiratory symptoms on two consecutive days, a decrease of more than 15% in the FEV₁ from the level at randomization after the use of albuterol, or a 2-point worsening in the Likert score for cough by the investigators at their discretion on the basis of general clinical worsening. For the latter exacerbation, sputum-cell counts were not known to the treating physician at the time this decision was made and were not considered in the definition of exacerbations.

Exacerbations, unless accompanied by sputum neutrophilia, were treated with 30 mg of prednisone for 7 days. During this time, the patient was withdrawn from the study and was seen again at 2 and 4 weeks. If the exacerbation was accompanied by neutrophilic airway inflammation (total cell count, >15×10⁶ per gram of sputum; neutrophils, >80%), it was treated with 500 mg of amoxicillin-clavulanic acid twice daily for 10 days; patients with neutrophilic exacerbations were not withdrawn from the study, and they continued with the protocol for prednisone reduction.

PROCEDURES

Spirometry was performed according to the recommendations of the American Thoracic Society,⁶ and predicted values were obtained according to the criteria of Crapo et al.⁷ Asthma control was assessed with the use of the validated Juniper Asthma Control Questionnaire.⁴ In addition, symptoms of coughing, wheezing, chest tightness, and shortness of breath were evaluated for the 7 days before each visit on a 7-point Likert scale.⁵ Sputum was induced and processed, as described by Pizzichini et al.⁸ Airway responsiveness to methacholine was measured with the use of the tidal-

breathing method described by Cockcroft et al.⁹ after withholding beta-agonists for 24 hours.

STATISTICAL ANALYSIS

The number of patients needed for the study was based on the primary outcome of the proportion of patients with exacerbations in each study group. It was expected that when the prednisone dose was reduced to 50%, exacerbations would occur in all patients in the placebo group and in not more than four patients in the mepolizumab group. The study had a power of 90% to detect this difference. A second primary outcome was the magnitude of the reduction in the dose of prednisone. This outcome was calculated as follows: [(starting dose – final dose without exacerbation) ÷ maximum possible dose reduction per protocol] × 100.

All primary analyses were performed according to the intention-to-treat principle. Since two patients who underwent randomization in error did not have sputum eosinophilia, we included these two patients in the primary analysis and then performed another analysis from which they were excluded.

Baseline characteristics and demographic data were summarized with the use of descriptive statistics. Between-group comparisons of normally distributed data were performed with the use of unpaired t-tests; comparisons between non-normally distributed data were made with the use of the Mann-Whitney U test. Within-group comparisons of normally distributed data were performed with the use of paired t-tests. Proportions were analyzed with the use of Fisher's exact test. Cumulative probability and time to exacerbation were compared by Kaplan-Meier analysis and the Mantel-Cox log-rank test. All tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the use of SPSS software, version 15.0 (SPSS).

RESULTS

PATIENTS

Nineteen of the 20 patients completed the study. One patient in the mepolizumab group was withdrawn from the study after the third infusion because of heart failure but was included in the analysis. Thus, the main analyses included 20 patients, and the per-protocol analysis included only the 18 subjects who had airway eosinophilia at baseline.

PRIMARY OUTCOMES

Exacerbations

There were 12 asthma exacerbations in the placebo group. Of these, nine were associated with sputum eosinophilia, and three were associated with sputum neutrophilia; two of the latter occurred in a patient who was eventually treated for an exacerbation associated with sputum eosinophilia. Thus, 10 of the 11 patients in the placebo group had exacerbations that led to treatment with prednisone or antibiotics. In contrast, there were two events in the mepolizumab group (one neutrophilic exacerbation and one withdrawal due to an adverse event) ($P=0.008$). Exacerbations were identified by a decline in the FEV₁ and additional criteria in seven patients (one in the mepolizumab group and six in the placebo group), by an increase in β_2 -agonist rescue (three in the placebo group), and by nocturnal symptoms (one in the placebo group). A change in the Likert scale alone or physician discretion was not used in any patient to identify an exacerbation or initiate a change in the dose of prednisone (Table 3 in the Supplementary Appendix). The median time to exacerbation (regardless of the type of bronchitis) was 20 weeks in the mepolizumab group and 12 weeks in the placebo group ($P=0.003$) (Fig. 2).

Reduction in Prednisone Dose

In the mepolizumab group, patients had a mean (\pm SD) reduction in the use of prednisone of $83.8 \pm 33.4\%$ of the maximum possible reduction per protocol, as compared with $47.7 \pm 40.5\%$ in the placebo group ($P=0.04$). In absolute terms, the mean dose of prednisone was reduced from 11.9 to 3.9 mg in the mepolizumab group and from 10.7 to 6.4 mg in the placebo group (median reduction in the two groups, from 10 to 5 mg) ($P=0.11$) (Table 2 in the Supplementary Appendix).

Prespecified Subgroup Analyses

Data for 8 of 10 patients in the placebo group who had an exacerbation accompanied by sputum eosinophilia were censored at the time of exacerbation, whereas none of the patients in the mepolizumab group had an exacerbation associated with sputum eosinophilia ($P=0.02$) (Table 3 in the Supplementary Appendix). There were three exacerbations in the placebo group that were associated with sputum neutrophilia. In the mepolizumab group, there were five episodes of increased numbers of sputum neutrophils (in four patients) during routine visits, but the episodes

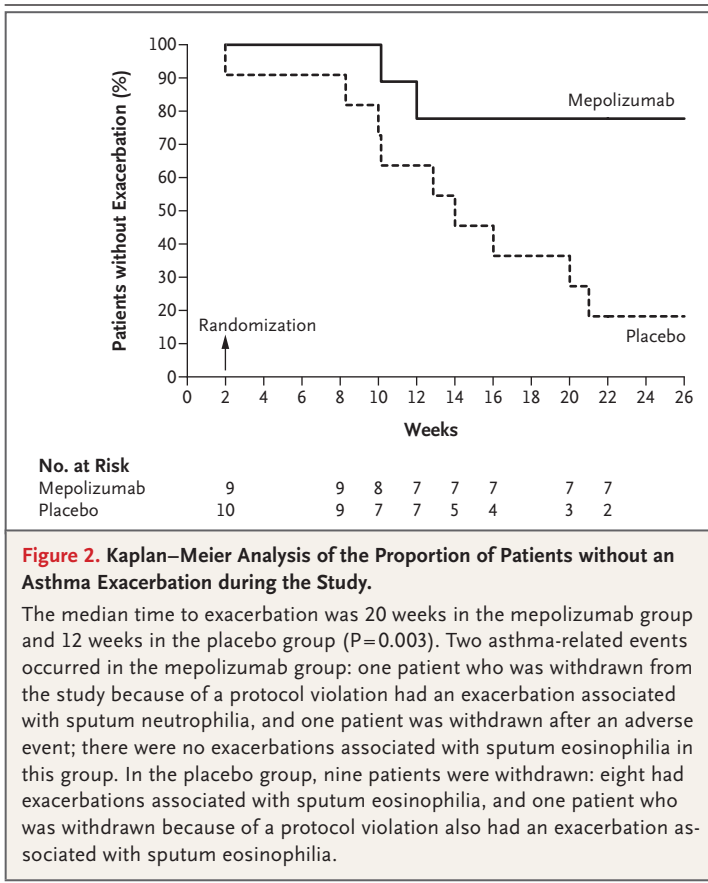


Figure 2. Kaplan–Meier Analysis of the Proportion of Patients without an Asthma Exacerbation during the Study.

The median time to exacerbation was 20 weeks in the mepolizumab group and 12 weeks in the placebo group ($P=0.003$). Two asthma-related events occurred in the mepolizumab group: one patient who was withdrawn from the study because of a protocol violation had an exacerbation associated with sputum neutrophilia, and one patient was withdrawn after an adverse event; there were no exacerbations associated with sputum eosinophilia in this group. In the placebo group, nine patients were withdrawn: eight had exacerbations associated with sputum eosinophilia, and one patient who was withdrawn because of a protocol violation also had an exacerbation associated with sputum eosinophilia.

were not associated with a change in the measures that defined an exacerbation and thus were not treated.

In the mepolizumab group, there was a mean reduction in the use of prednisone of $94.3 \pm 12.9\%$ of the maximum possible reduction per protocol, as compared with $47.5 \pm 42.2\%$ in the placebo group ($P=0.01$).

PRESPECIFIED SECONDARY OUTCOMES

There was an imbalance in the baseline level of sputum eosinophils, with a significantly higher level in the mepolizumab group (18.8%) than in the placebo group (4.3%, $P=0.03$).

Phase 1 and Phase 3

A single infusion of mepolizumab was associated with a reduction in the number of eosinophils to within normal limits in sputum ($P=0.005$) and blood ($P=0.004$). The levels remained within normal limits after reductions in the dose of prednisone for up to 8 weeks after the last infusion of mepolizumab ($P=0.01$). In contrast, a reduction in

the dose of prednisone in the placebo group was associated with a significant increase in the number of eosinophils in sputum and blood (Fig. 3 and Table 2). There was no significant effect of mepolizumab on cell types other than eosinophils in sputum or blood (Table 4 in the Supplementary Appendix), except for a significant reduction in the number of lymphocytes in sputum 4 weeks after the fifth infusion ($P=0.001$). Mepolizumab treatment was associated with a modest improvement in FEV₁ (mean, 300 ml), a nonsignificant improvement in asthma symptoms, and a significant improvement in scores on the Juniper Asthma Control Questionnaire ($P=0.01$) (Table 2, and Fig. 3C in the Supplementary Appendix).

Adverse Events

One patient in the mepolizumab group had progressive shortness of breath after receiving three infusions of the drug and was removed from the study. Investigators who were unaware of study-group assignments determined that this patient had preexisting coronary artery disease; the breathlessness was attributed to heart failure due to ischemic cardiomyopathy. The patient did not undergo endocardial biopsy or cardiac magnetic resonance imaging to rule out eosinophilic cardiomyopathy. One patient in the placebo group died suddenly at home 6 months after completing the full study. On autopsy, the cause of death was identified as sudden cardiac arrest possibly due to a ventricular tachyarrhythmia and was not ascribed to worsening asthma. One patient in the mepolizumab group reported having aches and tiredness when the prednisone dose was reduced to 2.5 mg. One patient in the placebo group had hypoadrenalism during the prednisone reduction from 12.5 to 5 mg per day (as demonstrated by a blunted cortisol response to a short corticotropin stimulation test). There were no other serious adverse events. There were no significant abnormalities in blood chemical values attributable to mepolizumab.

DISCUSSION

Our data show that in a rare subgroup of patients with asthma who continue to have sputum eosinophilia even after treatment with oral prednisone and high-dose inhaled corticosteroids, treatment with a humanized monoclonal antibody against interleukin-5 allows a reduction in the dose of

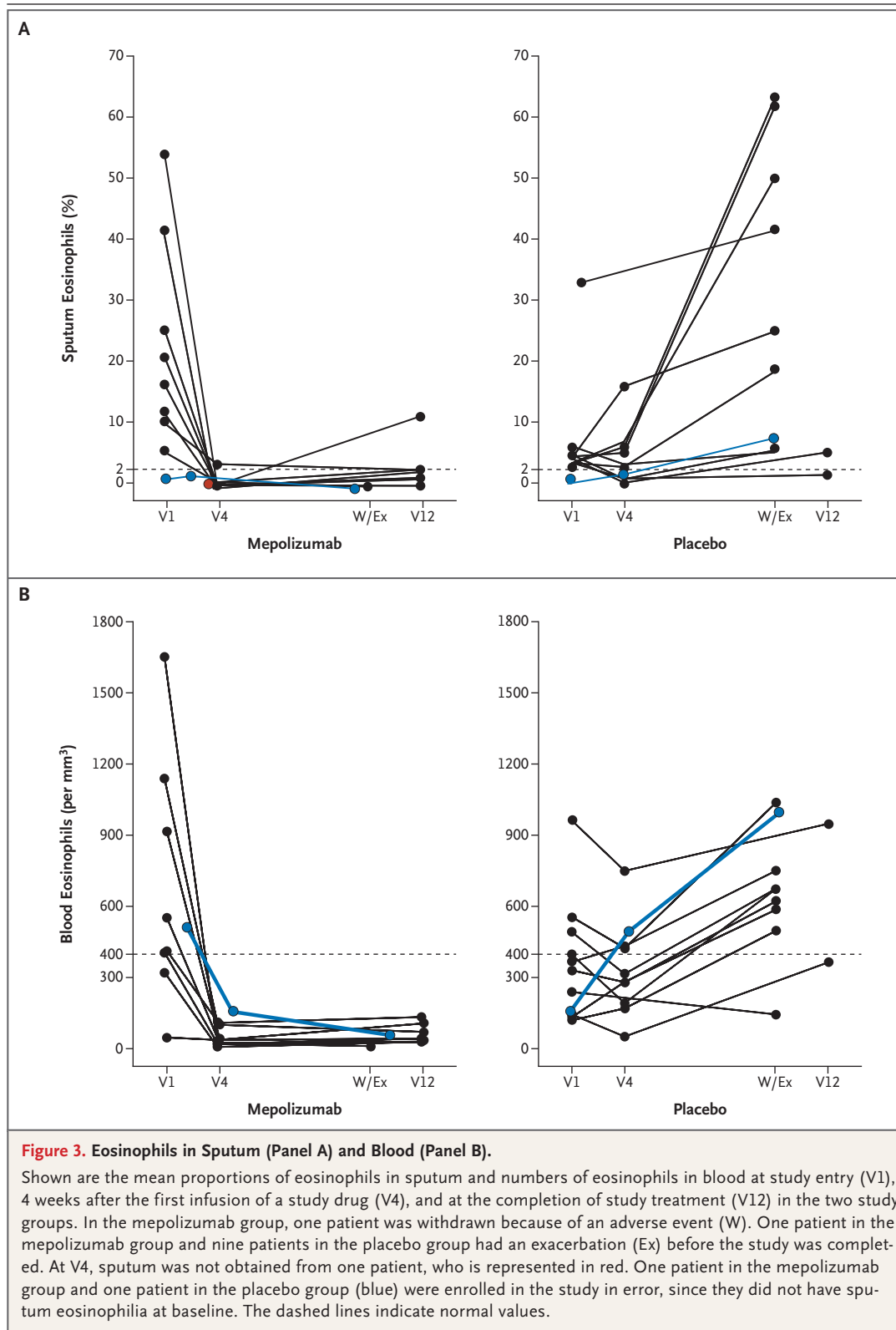


Table 2. Primary Outcomes.*

Variable	Mepolizumab				Placebo				
	Visit 1 (Baseline)	Visit 4 (4 Wk after First Dose)	Visit 12 (4 Wk after Last Dose)	Visit 14 (8 Wk after Last Dose)	Visit 1 (Baseline)	Visit 4 (4 Wk after First Dose)	Visit 12 (4 Wk after Last Dose)	Visit 14 (8 Wk after Last Dose)	Exacerbation 4 Wk after Exacerbation
No. of patients	9	9	7	7	11	10	2	2	9
Sputum eosinophils (%)									
Median	16.6	0†	1.3‡	0.3‡	4.0	3.0	3.2	5.0	25.3
Range	1.6–54.3	0–4.0	0–11.3	0–4.6	0–35.3	0–16.3	1.3–5.0	1.0–9.0	5.0–63.7
Blood eosinophils (per mm ³)	664.4±492.5	49.5±37.5‡	64.5±37.9‡	76.3±39.4‡	352.1±253.7	295.8±207.4	657.0±413.2	1224.0±1383.0	655.5±254.8
FEV ₁ after bronchodilation									
Value (liters)	2.0±0.9	2.1±1.0	2.4±1.1‡	2.3±0.9	2.2±0.9	2.3±0.9	2.3±0.4	2.3±0.4	2.0±1.0
% of predicted value	66.6±18.3	69.7±17.7	71.9±17.3‡	70.3±13.2‡	74.3±17.8	75.6±17.0	78.4±20.9	78.1±19.2	60.9±20.7
Juniper Asthma Control Questionnaire§	1.9±0.8	1.3±0.9†	1.2±0.8†	1.3±0.9†	1.8±0.9	1.6±0.9	1.2±0.5	1.2±0.3	2.0±1.0
Cough score¶	6.0±0.8	5.2±0.8†	5.3±1.0†	5.5±1.0	6.3±1.0	5.2±1.2	NA	NA	5.8±1.1
Symptoms score	29.4±2.9	28.7±4.9	31.6±2.3	30.1±4.0	29.8±5.1	30.8±2.9	33.2±1.6	32.5±3.5	27.2±4.2

* Plus-minus values are means ±SD. FEV₁ denotes forced expiratory volume in 1 second, and NA not applicable.

† P<0.05 for the comparison with the baseline value.

‡ P<0.05 for the comparison with the corresponding change from baseline in the placebo group.

§ The Juniper Asthma Control Questionnaire score ranges from 0 to 6, with higher scores indicating worse control.

¶ The cough score, which was measured only in patients without current asthma at screening, ranges from 1 to 7, with lower scores indicating a greater severity of symptoms.

|| The symptoms score ranges from 7 to 35, with lower scores indicating greater severity of symptoms. This score consists of a composite rating of shortness of breath, chest tightness, wheezing, cough, and sputum production, each graded on a 7-point Likert scale.

prednisone without the development of asthma exacerbations. These results are contrary to the negative results of earlier studies with a similar antibody^{1-3,10} in patients with more common forms of asthma. However, our findings support results of studies involving patients with the hypereosinophilic syndrome¹¹⁻¹³ and those of two case-report abstracts involving patients with asthma with sputum eosinophilia¹⁴ and the hypereosinophilic syndrome with asthma.¹⁵

In our patients with adult-onset asthma, sputum eosinophilia that persisted in the presence of oral and inhaled corticosteroid treatment was reversed by the anti-interleukin-5 treatment, accompanied by clinical improvement. In contrast, in the earlier studies, either sputum eosinophils were not measured or there was little or no sputum eosinophilia at the onset of the study.^{2,3} None of the previous studies reported the effect of this treatment on the small subgroup of patients with baseline airway eosinophilia. It is thus possible that the reason for the lack of clinical benefit in previous trials was that the majority of patients did not have the clinical phenotype of persistent airway eosinophilia despite corticosteroid treatment, as did the patients in our study.

Our study had some substantial limitations. First, there was a higher sputum eosinophil count at baseline in the mepolizumab group. We cannot discount the possibility that the patients who had a response to mepolizumab were those with the highest numbers of eosinophils in sputum despite corticosteroid treatment. Second, although we demonstrated a substantial prednisone-sparing effect in the mepolizumab group, there was no significant difference in the more clinically meaningful outcome of the final prednisone doses in the two study groups. Third, we relied on past objective evidence of asthma as indicated by variable airflow limitation. Since most patients had had frequent exacerbations in the past and were receiving a maintenance dose of a long-acting bronchodilator or had moderate airflow obstruction at baseline, we did not retest for albuterol reversibility or methacholine airway hyperresponsiveness in all patients at baseline. Fourth, the patients we studied represent only a small proportion of patients who have asthma and persistent sputum eosinophilia, so our results would not apply to most patients with asthma. Fifth, despite our efforts, some investigators may not have remained unaware of study-group assignments be-

cause they were aware of sputum-cell counts. Sixth, the study was small and cannot be considered clinically directive.

In summary, intravenous mepolizumab reduced the number of eosinophils in blood and sputum and was associated with prednisone sparing in patients with asthma who had sputum eosinophilia despite the use of oral prednisone and high-dose inhaled corticosteroid treatment. Our small pilot study is potentially clinically directive and highlights the importance of selecting patients with airway eosinophilia for the study of the use of anti-eosinophil drugs in asthma.

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Dr. Nair reports receiving lecture fees from Merck and Schering-Plough; Dr. Inman, research grants from GlaxoSmithKline, Amgen, and AstraZeneca; Drs. M. Pizzichini and E. Pizzichini, lecture fees from AstraZeneca and GlaxoSmithKline; Dr. E. Pizzichini, consulting fees from AstraZeneca, GlaxoSmithKline, Novartis, and Nycomed; Dr. Hargreave, consulting fees from Methapharm, Ception, and Schering-Plough; and Dr. O'Byrne, consulting fees from AstraZeneca, Biolipox, GlaxoSmithKline, Resistentia, Topigen, Merck, Nycomed, and Wyeth, lecture fees from AstraZeneca, Chiesi, GlaxoSmithKline, Nycomed, and Ono Pharmaceutical, and research grants from Alexion, Genentech, Medimmune, Merck, Wyeth, and Schering. Drs. Nair and Hargreave and Ms. Efthimiadis report being listed on a patent application for a sputum-filtration device. No other potential conflict of interest relevant to this article was reported.

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