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Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

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ABSTRACT

BACKGROUND

Many patients with severe asthma require regular treatment with oral glucocorticoids despite the use of high-dose inhaled therapy. However, the regular use of systemic glucocorticoids can result in serious and often irreversible adverse effects. Mepolizumab, a humanized monoclonal antibody that binds to and inactivates interleukin-5, has been shown to reduce asthma exacerbations in patients with severe eosinophilic asthma.

METHODS

In a randomized, double-blind trial involving 135 patients with severe eosinophilic asthma, we compared the glucocorticoid-sparing effect of mepolizumab (at a dose of 100 mg) with that of placebo administered subcutaneously every 4 weeks for 20 weeks. The primary outcome was the degree of reduction in the glucocorticoid dose (90 to 100% reduction, 75 to less than 90% reduction, 50 to less than 75% reduction, more than 0 to less than 50% reduction, or no decrease in oral glucocorticoid dose, a lack of asthma control during weeks 20 to 24, or withdrawal from treatment). Other outcomes included the rate of asthma exacerbations, asthma control, and safety.

RESULTS

The likelihood of a reduction in the glucocorticoid-dose stratum was 2.39 times greater in the mepolizumab group than in the placebo group (95% confidence interval, 1.25 to 4.56; $P=0.008$). The median percentage reduction from baseline in the glucocorticoid dose was 50% in the mepolizumab group, as compared with no reduction in the placebo group ($P=0.007$). Despite receiving a reduced glucocorticoid dose, patients in the mepolizumab group, as compared with those in the placebo group, had a relative reduction of 32% in the annualized rate of exacerbations (1.44 vs. 2.12, $P=0.04$) and a reduction of 0.52 points with respect to asthma symptoms ($P=0.004$), as measured on the Asthma Control Questionnaire 5 (in which the minimal clinically important difference is 0.5 points). The safety profile of mepolizumab was similar to that of placebo.

CONCLUSIONS

In patients requiring daily oral glucocorticoid therapy to maintain asthma control, mepolizumab had a significant glucocorticoid-sparing effect, reduced exacerbations, and improved control of asthma symptoms. (Funded by GlaxoSmithKline; SIRIUS ClinicalTrials.gov number, NCT01691508.)

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ASTHMA IS A COMMON CHRONIC INflammatory disease of the airways that affects 5 to 10% of adults and children. Although the disease is well controlled with inhaled therapy in most patients, approximately 10% have severe asthma that is associated with substantial morbidity, mortality, and economic effects.¹ Patients with severe asthma have complex treatment requirements, which in 30 to 40% of such patients include the regular use of oral glucocorticoids to control their asthma.²⁻⁴ Such therapy can result in serious and often irreversible adverse effects.^{5,6} Current treatments with glucocorticoid-sparing properties are not recommended in patients with severe asthma because of their high risk–benefit ratio.⁷ Therefore, such patients would benefit from safe glucocorticoid-sparing treatments.

Mepolizumab is a humanized monoclonal antibody that binds to and inactivates interleukin-5, a cytokine that recruits eosinophils from the bone marrow and promotes the persistence and activation of these cells.^{8,9} Mepolizumab has been shown to reduce the frequency of asthma exacerbations in patients with severe eosinophilic asthma, including some who were already taking oral glucocorticoids.^{10,11} In addition, a proof-of-concept study involving 20 patients with eosinophilic asthma showed that the intravenous administration of mepolizumab was effective in reducing the maintenance dose of prednisone while preventing exacerbations.¹²

In this study, called the Steroid Reduction with Mepolizumab Study (SIRIUS), we compared the effect of mepolizumab adjunctive subcutaneous therapy with that of placebo in reducing the use of maintenance oral glucocorticoids while maintaining asthma control in patients with severe eosinophilic asthma.

METHODS

STUDY DESIGN

This multicenter, randomized, placebo-controlled, double-blind, parallel-group study consisted of four phases: optimization of the oral glucocorticoid regimen, induction, reduction in the oral glucocorticoid dose, and maintenance (Fig. 1A). The optimization phase was designed to establish the lowest dose of maintenance oral glucocorticoids associated with acceptable asthma control. During this phase, the oral glucocorticoid dose was reduced weekly until there was an exac-

erbation in asthma symptoms or an increase of at least 0.5 points from the visit 1 score on the Asthma Control Questionnaire 5 (ACQ-5)¹³ (on which scores range from 0 to 6, with higher scores indicating poorer control and 0.5 points representing the minimal clinically important difference) (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

After optimization of the oral glucocorticoid regimen, patients underwent randomization in a 1:1 ratio to receive mepolizumab (at a dose of 100 mg) or placebo by subcutaneous injection and entered the induction phase (weeks 0 to 4), during which they received the assigned study drug and continued to receive their optimized dose of oral glucocorticoids. During the reduction phase (weeks 4 to 20), the oral glucocorticoid dose was reduced according to a pre-specified schedule by 1.25 to 10 mg per day every 4 weeks (Tables S2 and S3 in the Supplementary Appendix) on the basis of asthma control and symptoms of adrenal insufficiency. During the maintenance phase (weeks 20 to 24), no further adjustment was made in the oral glucocorticoid dose. In addition, a follow-up safety visit was scheduled at week 32. Throughout the study, patients continued to receive the same maintenance regimen of asthma drugs that they were receiving during the optimization phase. Patients recorded data on peak expiratory flow, asthma symptoms, and ACQ-5 scores in an electronic diary (eDiary, PHT).

PATIENTS

Eligible patients had at least a 6-month history of maintenance treatment with systemic glucocorticoids (5 to 35 mg per day of prednisone or its equivalent) before entering the study. The presence of eosinophilic inflammation was determined by a blood eosinophil level of either 300 cells or more per microliter during the 12-month period before screening or 150 cells or more per microliter during the optimization phase. All patients were treated with high-dose inhaled glucocorticoids and an additional controller. Detailed descriptions of the inclusion and exclusion criteria are provided in the study protocol, available at NEJM.org. All patients provided written informed consent.

STUDY TREATMENTS

Mepolizumab or placebo was administered subcutaneously once every 4 weeks until week 20.

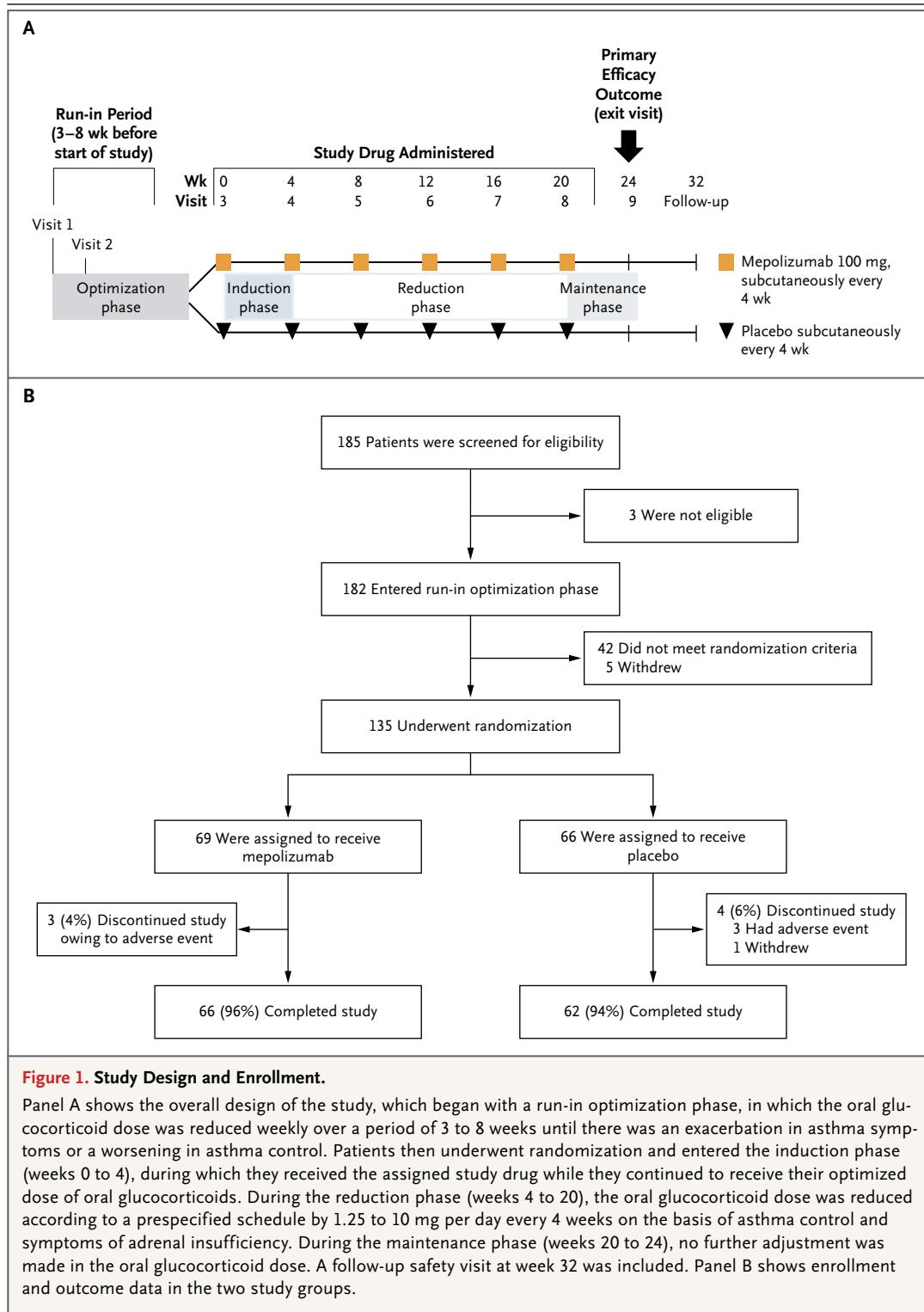


Figure 1. Study Design and Enrollment.

Panel A shows the overall design of the study, which began with a run-in optimization phase, in which the oral glucocorticoid dose was reduced weekly over a period of 3 to 8 weeks until there was an exacerbation in asthma symptoms or a worsening in asthma control. Patients then underwent randomization and entered the induction phase (weeks 0 to 4), during which they received the assigned study drug while they continued to receive their optimized dose of oral glucocorticoids. During the reduction phase (weeks 4 to 20), the oral glucocorticoid dose was reduced according to a prespecified schedule by 1.25 to 10 mg per day every 4 weeks on the basis of asthma control and symptoms of adrenal insufficiency. During the maintenance phase (weeks 20 to 24), no further adjustment was made in the oral glucocorticoid dose. A follow-up safety visit at week 32 was included. Panel B shows enrollment and outcome data in the two study groups.

The 1:1 randomization was performed with the use of a centralized, computer-generated, permuted-block design, which was stratified according to country and duration of previous use of oral glucocorticoids (<5 years vs. ≥5 years). At each study center, formulations of mepolizumab and placebo were prepared by staff members who were aware of study-group assignments but

were not involved in study assessments. The two preparations were identical in appearance and were administered in a blinded fashion. Staff members checked patients' eDiary entries to determine whether they were taking the oral glucocorticoid dose according to the protocol.

STUDY ASSESSMENTS AND PROCEDURES

A clinically significant exacerbation was defined as a worsening of asthma leading to the doubling (or more) of the existing maintenance dose of oral glucocorticoids for 3 or more days or hospital admission or an emergency department visit for asthma treatment. Staff members measured the forced expiratory volume in 1 second (FEV₁) before and after bronchodilation according to international standards, using equipment available at each study site.¹³ Asthma control and quality of life were assessed by means of the ACQ-5 and St. George's Respiratory Questionnaire (SGRQ) (on which scores range from 0 to 100, with higher scores indicating worse functioning and a change of 4 units considered to be clinically relevant).^{14,15}

EFFICACY OUTCOMES

The primary efficacy outcome was the percentage reduction in the daily oral glucocorticoid dose during weeks 20 to 24 as compared with the dose determined during the optimization phase, on the basis of using the following categories: 90 to 100% reduction, 75 to less than 90% reduction, 50 to less than 75% reduction, more than 0 to less than 50% reduction, and no decrease in the oral glucocorticoid dose, lack of asthma control during weeks 20 to 24, or withdrawal from treatment. Secondary prespecified outcomes were the proportions of patients who had a reduction of 50% or more in the oral glucocorticoid dose, who had a reduction in the oral glucocorticoid dose to a value of 5.0 mg or less per day, and who had a total cessation in oral glucocorticoid use and the median percentage reduction in the oral glucocorticoid dose. Other outcomes included the annualized rates of asthma exacerbations, the mean change from baseline in the FEV₁ before and after bronchodilation, ACQ-5 score, SGRQ score, safety, and immunogenicity.

STUDY OVERSIGHT

The study was designed by the sponsor, Glaxo-SmithKline, in collaboration with the clinical

investigators. Employees of the sponsor analyzed the data, and all the authors reviewed the data and participated in discussions. The first and last authors drafted the manuscript, which was revised by all the other authors. Editorial support in the form of preparation of the manuscript for submission was provided by Gardiner-Caldwell Communications and was funded by the sponsor. The protocol was approved by the institutional review board at each participating center. All the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of this report to the study protocol.

STATISTICAL ANALYSIS

The sample-size calculation was based on the proportional-odds model.¹⁶ We estimated that with a sample of 120 patients, the study would have a power of 90% to detect an increase of 25 percentage points in the proportion of patients who had a reduction of 50% or more in the oral glucocorticoid dose, at a two-sided 5% significance level. On the assumption that such a reduction would occur in 48% of the patients in the placebo group, our calculation implied that 73% of patients in the mepolizumab group would have this reduction. These proportions were associated with an odds ratio of 2.9 for a lower category of glucocorticoid use in the mepolizumab group, than in the placebo group.

The primary analysis was performed in the intention-to-treat population, which included all patients who underwent randomization. We used a proportional-odds model to analyze the primary outcome for the above-mentioned categories of reduction in the oral glucocorticoid dose, with covariates of region, duration of use of oral glucocorticoids (<5 years vs. ≥5 years), and baseline oral glucocorticoid dose. We analyzed categories of percentage reduction, rather than the proportions of patients who had a specific reduction, to increase the discrimination of response, and we used the proportional-odds model because it allows for adjustment for covariates. We used a binary logistic-regression model with adjustment for covariates to analyze the proportion of patients with specific reductions in the oral glucocorticoid dose. The median percentage reduction in dose was analyzed with the use of the Wilcoxon test.

We used a negative binomial generalized linear model with a log-link function with adjust-

ment for covariates to analyze the rate of clinically significant exacerbations.¹⁷ Changes from baseline to week 24 in the FEV₁, ACQ-5 score, SGRQ score, and blood eosinophil count were analyzed with the use of a mixed-model, repeated-measures analysis after adjustment for covariates. A prespecified log transformation was applied to blood eosinophil counts before analysis. All analyses were performed with the use of SAS software, version 9 (SAS Institute).

RESULTS

PATIENTS

Of the 185 patients who were screened, 135 underwent randomization and were included in the intention-to-treat population. Seven patients (3 in the mepolizumab group and 4 in the placebo group) withdrew from the study prematurely, primarily because of adverse events (Fig. 1B). Table 1 shows the characteristics of the pa-

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N = 66)	Mepolizumab (N = 69)
Mean age (range) — yr	50 (28–70)	50 (16–74)
Female sex — no. (%)	30 (45)	44 (64)
Body-mass index†	29.5±6.0	27.8±5.9
Former smoker — no. (%)	25 (38)	28 (41)
Duration of asthma — yr	20.1±14.4	17.4±11.8
Median daily oral glucocorticoid dose — mg‡		
At screening	15.0	12.5
During optimization phase	12.5	10.0
Duration of oral glucocorticoid use ≥5 yr — no. (%)	31 (47)	34 (49)
FEV ₁ before bronchodilation		
Mean — liters	2.00±0.82	1.90±0.66
Percent of predicted value	57.8±18.5	59.6±17.0
FEV ₁ :FVC ratio before bronchodilation — %§	61±11.7	63±12.4
Percent reversibility of FEV ₁	24.8±18.1	27.3±17.4
ACQ-5 score¶	2.0±1.2	2.2±1.3
SGRQ score	45±18	50±18
Geometric mean IgE on log _e scale — U/ml	114±1	117±1
Geometric mean blood eosinophil count on log _e scale — cells/μl**	230±1001	250±1245
Severe exacerbations in previous year — no./patient	2.9±2.8	3.3±3.4
Exacerbations in the previous year requiring hospitalization — no. (%)	9 (14)	14 (20)
History of asthma-related intubation — no. (%)	3 (5)	2 (3)

* Plus-minus values are means (or geometric means) ±SD unless otherwise stated. There were no significant between-group differences at baseline with the exception of sex (P=0.04). Percentages may not total 100 because of rounding. More details about baseline characteristics are provided in Table S4 in the Supplementary Appendix. FEV₁ denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

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

‡ Doses are provided as prednisone equivalents.

§ The FEV₁:FVC ratio was calculated by dividing the FEV₁ by the FVC and then multiplying by 100 to express the value as a percentage.

¶ Scores on the Asthma Control Questionnaire 5 (ACQ-5) range from 0 to 6, with higher scores indicating worse control of asthma; a change of 0.5 points is the minimal clinically important difference.

|| Scores on St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with higher scores indicating worse function; a change of 4 units is considered to be clinically relevant.

** Values below the lower limit of quantification (LLQ) were replaced by 50% of the LLQ.

tients at baseline. (More complete data with respect to demographic and clinical characteristics are provided in Table S4 in the Supplementary Appendix.)

EFFICACY

In the prespecified primary outcome, more patients in the mepolizumab group than in the placebo group had a reduction of 90 to 100% in the oral glucocorticoid dose (23% vs. 11%) and a reduction of 70 to less than 90% (17% vs. 8%). In contrast, more patients in the placebo group than in the mepolizumab group had no reduction in the oral glucocorticoid dose, had a lack of asthma control, or withdrew from the study (56% vs. 36%). These analyses resulted in an overall odds ratio for a reduction in the oral glucocorticoid dose category in the mepolizumab group of 2.39 (95% confidence interval [CI], 1.25

to 4.56; $P=0.008$) (Table 2). The median percentage reduction from baseline in the daily oral glucocorticoid dose was 50% among patients in the mepolizumab group, as compared with no reduction among those in the placebo group ($P=0.007$) (Fig. 2A).

Treatment with mepolizumab, as compared with placebo, resulted in significant improvements in all secondary outcomes of oral glucocorticoid reduction ($P\leq 0.03$), except for the outcome of a total cessation of daily oral glucocorticoids ($P=0.41$) (Table 2). Mean and median reductions from baseline in the oral glucocorticoid dose are provided in Table S5 in the Supplementary Appendix.

OTHER PRESPECIFIED OUTCOMES

The annualized rates of exacerbations were 1.44 per year in the mepolizumab group and 2.12 per

Table 2. Primary and Secondary Outcomes.

Outcome	Placebo (N=66)	Mepolizumab (N=69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		
Secondary outcomes				
Reduction in daily oral glucocorticoid dose of $\geq 50\%$ — no. (%)‡	22 (33)	37 (54)	2.26 (1.10–4.65)	0.03
Reduction in daily oral glucocorticoid dose to a level ≤ 5 mg — no. (%)‡	21 (32)	37 (54)	2.45 (1.12–5.37)	0.02
Reduction of 100% in oral glucocorticoid dose — no. (%)‡	5 (8)	10 (14)	1.67 (0.49–5.75)	0.41
Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI)§	0.0 (–20.0 to 33.3)	50.0 (20.0 to 75.0)	NA	0.007

* Odds ratios are for the mepolizumab group as compared with the placebo group. NA denotes not applicable.

† Data for the primary outcome were analyzed with the use of a proportional-odds model (ordered multinomial logistic regression), with terms for study group, region, duration of oral glucocorticoid use at baseline (<5 yr vs. ≥ 5 yr), and baseline oral glucocorticoid dose during the optimization phase.

‡ Data were analyzed with the use of a binary logistic-regression model with terms for study group, region, duration of oral glucocorticoid use at baseline (<5 yr vs. ≥ 5 yr), and baseline oral glucocorticoid dose during the optimization phase.

§ The median difference and associated confidence intervals were calculated with the use of the Hodges–Lehman estimation. P values were calculated with the use of a Wilcoxon rank-sum test. For patients who withdrew from the study before the maintenance phase, a value equal to the minimum percent reduction in oral glucocorticoid use for all patients was imputed for the analysis.

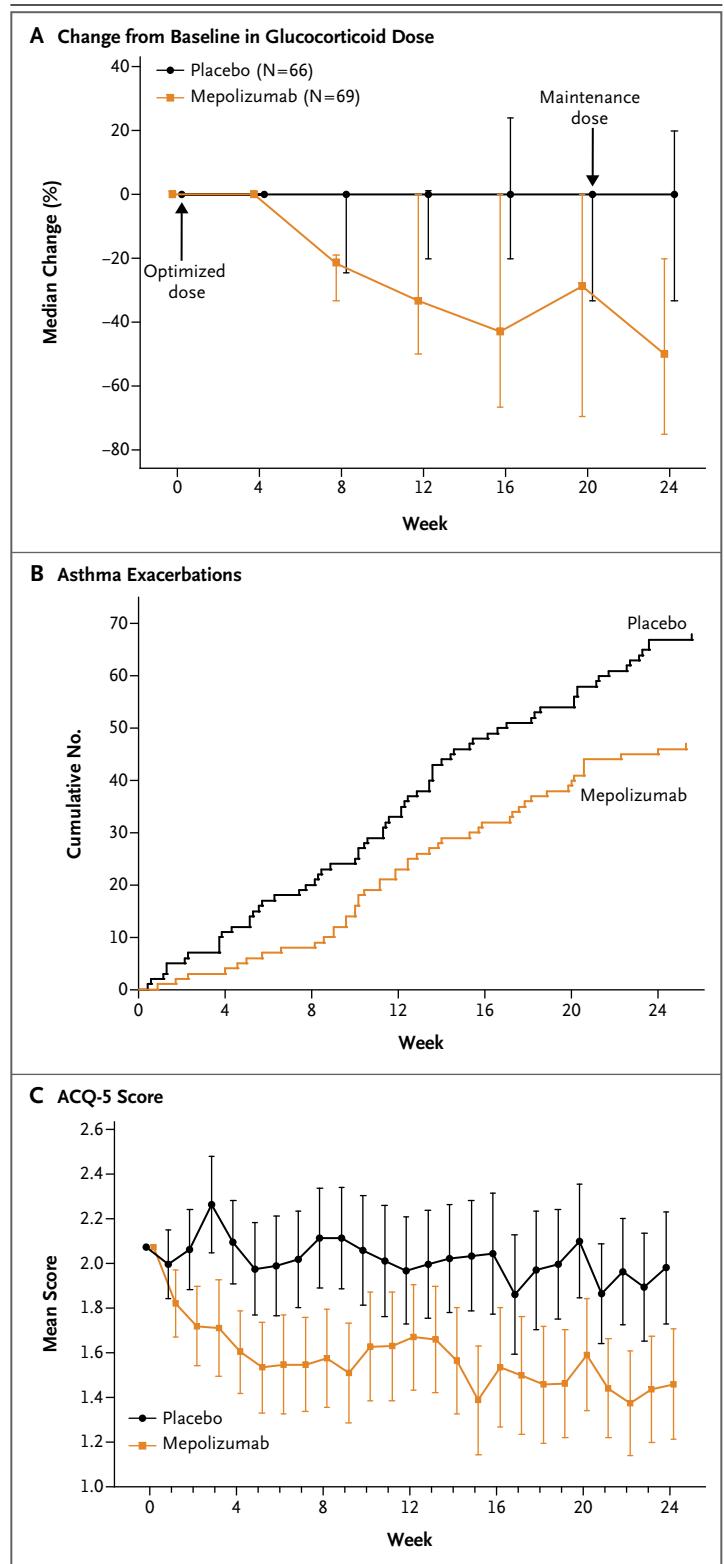
Figure 2. Changes in Oral Glucocorticoid Dose, Rate of Exacerbations, and Asthma Control.

Panel A shows the median percentage reduction from baseline in the daily glucocorticoid dose in the two study groups. At 24 weeks, the median percentage reduction was 50% in the mepolizumab group, and there was no reduction in the placebo group ($P=0.007$). The I bars represent 95% confidence intervals. Panel B shows the cumulative rate of clinically significant asthma exacerbations, with a relative reduction of 32% in the mepolizumab group, as compared with the placebo group, at week 24 ($P=0.04$). Panel C shows changes in responses on the Asthma Control Questionnaire 5 (ACQ-5). The score on the ACQ-5 represents the mean of responses to five questions about the frequency or severity of symptoms during the previous week, with each response scored on a scale of 0 to 6 and higher scores indicating poorer control; the minimal clinically important difference for the mean score is 0.5 points. Improvements were observed as early as week 2 in the mepolizumab group, an effect that was sustained up to week 24 ($P=0.004$). The I bars represent 95% confidence intervals around the least-square means.

year in the placebo group (rate ratio, 0.68; 95% CI, 0.47 to 0.99; $P=0.04$) (Fig. 2B). Improvements in ACQ-5 scores (as indicated by lower scores) were observed as early as week 2 in the mepolizumab group and were sustained up to week 24 (between-group difference, -0.52 points; 95% CI, -0.87 to -0.17 ; $P=0.004$) (Fig. 2C). Improvement in the SGRQ score (as indicated by lower scores) was also noted at week 24 (between-group difference, -5.8 points; 95% CI, -10.6 to -1.0 ; $P=0.02$). At week 24, there was a nonsignificant trend toward greater changes from baseline in the FEV₁ before and after bronchodilation in the mepolizumab group than in the placebo group. There were between-group differences of 114 ml before bronchodilation ($P=0.15$) (Fig. S1 in the Supplementary Appendix) and 128 ml after bronchodilation ($P=0.06$). As compared with placebo, mepolizumab significantly reduced blood eosinophil counts throughout the study ($P<0.001$) (Fig. S2 in the Supplementary Appendix).

SAFETY

The incidence of nonasthma-related adverse events was 83% in the mepolizumab group and 91% in the placebo group (Table 3). The most frequently reported adverse events in the two study groups were headache and nasopharyngitis. Seven patients (four in the mepolizumab group and three in the placebo group) had systemic reactions, and six patients (four in the mepolizumab



group and two in the placebo group) had local injection-site reactions. During the study, there was one death (in the placebo group) from gas-

Table 3. Summary of Adverse Events.

Event	Placebo (N = 66)	Mepolizumab (N = 69)
	<i>no. of patients (%)</i>	
Adverse event		
Any	61 (92)	57 (83)
Nonasthma	60 (91)	57 (83)
Worsening of asthma	8 (12)	2 (3)
Related to study drug*	12 (18)	21 (30)
Leading to discontinuation of study drug or withdrawal from the study	3 (5)	3 (4)
Serious adverse event		
During treatment	12 (18)	1 (1)
Fatal	1 (2)	0

* This determination was made by investigators who were unaware of study-group assignments. Additional details regarding adverse events are provided in Table S6 in the Supplementary Appendix.

triointestinal hemorrhage and aspiration. Asthma exacerbations requiring hospitalization (in seven patients, all in the placebo group) and pneumonia (in three patients, all in the placebo group) were the most frequent serious adverse events. No serious cardiac, vascular, thromboembolic, or ischemic events were reported during the study. (Additional details about adverse events are provided in Table S6 in the Supplementary Appendix.)

IMMUNOGENICITY

Of the 135 patients in the two study groups, 6 (4%) had positive results on testing of post-baseline samples for anti-mepolizumab antibodies. Of the 6 patients, 5 had non-neutralizing antibodies at low titer (<32), and 1 patient had neutralizing antibodies after the administration of the first dose of mepolizumab (titer, 160) and at week 32 (titer, 640). No serious adverse events related to immunogenicity were reported.

DISCUSSION

In our study, among patients with severe eosinophilic asthma in whom doses of oral glucocorticoids had been reduced as much as possible before starting study treatment, those who received subcutaneous mepolizumab had significantly greater reductions in the maintenance oral glucocorticoid dose than did those receiving placebo. Mepolizumab also had a significantly beneficial

effect on exacerbations, asthma control, and quality of life, even though patients had a clinically relevant reduction in the dose of oral glucocorticoids.

A glucocorticoid-sparing effect of mepolizumab was seen by Nair et al. in a small pilot study, in which 20 patients were selected on the basis of elevated sputum eosinophil levels.¹² These patients were given 750 mg of mepolizumab or placebo intravenously every 4 weeks for 20 weeks, which resulted in a reduction of 84% in the prednisone dose in the mepolizumab group, as compared with a reduction of 48% in the placebo group. In our study, patients were selected on the basis of elevated levels of blood eosinophils, and mepolizumab was administered subcutaneously at a much lower dose (100 mg every 4 weeks). In common with Nair et al., we found that treatment with mepolizumab was associated with reduced exacerbations and improvements in measures of asthma control, despite a significant reduction in the use of oral glucocorticoids and a lower dose. Such improvements in asthma control were not observed in other studies of mepolizumab.^{10,11} This difference might be due to a more targeted selection of patients in our study or to a greater potential for symptomatic improvement in patients with oral glucocorticoid-dependent asthma. The similarity of the net effect of mepolizumab in our study and in the study by Nair et al. suggests that the selection of patients on the basis of blood eosinophil levels is adequate. It also provides evidence that mepolizumab did not lose efficacy when it was administered subcutaneously rather than intravenously and at a much lower dose^{11,18} than in the study by Nair et al.¹²

In our study, we incorporated an optimization phase for the patients' oral glucocorticoid regimen, since we wanted to establish that the patients genuinely required oral glucocorticoids for control of their asthma. This factor probably accounts for the lower placebo effect seen in our study, as compared with other glucocorticoid-reduction studies.^{12,19,20} In addition, a reduction in the glucocorticoid dose was allowed only in patients with stable ACQ-5 scores and in those for whom the investigator deemed that a reduction was appropriate. The validity of this approach was confirmed by the stability of the FEV₁ and ACQ-5 scores over the course of the study. As compared with a nonparametric analy-

sis of the primary outcome, our analysis that used categories for the response combined with the proportional-odds model was innovative in that it retained discrimination of response while allowing for covariate adjustment.

Our study has several potential limitations. First, we assumed a relationship between a worsening of symptoms and an increase in eosinophilic airway inflammation, which may not be valid for all patients.²¹ It is possible that if we had mandated evidence of eosinophilic inflammation in the optimization phase, a different drug effect would have been seen. Second, as with other studies of oral glucocorticoid withdrawal, our study was relatively short in duration and used a cautious strategy for oral glucocorticoid reduction.²¹ Longer and larger studies will be required to determine whether more complete withdrawal of oral glucocorticoids is pos-

sible and whether the outcomes reported in our trial are durable over an extended period of time.

In conclusion, patients with severe eosinophilic airway disease pose a treatment challenge for clinicians. Oral glucocorticoids, the only available treatment for these patients, can lead to serious and often irreversible side effects and complications.^{5,6} For this reason, patients often use lower maintenance doses than those that are required to completely suppress their symptoms. We found that the use of mepolizumab permitted a reduction in the oral glucocorticoid dose in a significant proportion of such patients.

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

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