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## Treatment of Patients with the Hypereosinophilic Syndrome with Mepolizumab

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### ABSTRACT

#### BACKGROUND

The hypereosinophilic syndrome is a group of diseases characterized by persistent blood eosinophilia, defined as more than 1500 cells per microliter with end-organ involvement and no recognized secondary cause. Although most patients have a response to corticosteroids, side effects are common and can lead to considerable morbidity.

#### METHODS

We conducted an international, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of an anti-interleukin-5 monoclonal antibody, mepolizumab, in patients with the hypereosinophilic syndrome. Patients were negative for the *FIP1L1-PDGFR*A fusion gene and required prednisone monotherapy, 20 to 60 mg per day, to maintain a stable clinical status and a blood eosinophil count of less than 1000 per microliter. Patients received either intravenous mepolizumab or placebo while the prednisone dose was tapered. The primary end point was the reduction of the prednisone dose to 10 mg or less per day for 8 or more consecutive weeks.

#### RESULTS

The primary end point was reached in 84% of patients in the mepolizumab group, as compared with 43% of patients in the placebo group (hazard ratio, 2.90; 95% confidence interval [CI], 1.59 to 5.26;  $P < 0.001$ ) with no increase in clinical activity of the hypereosinophilic syndrome. A blood eosinophil count of less than 600 per microliter for 8 or more consecutive weeks was achieved in 95% of patients receiving mepolizumab, as compared with 45% of patients receiving placebo (hazard ratio, 3.53; 95% CI, 1.94 to 6.45;  $P < 0.001$ ). Serious adverse events occurred in seven patients receiving mepolizumab (14 events, including one death; mean [±SD] duration of exposure, 6.7±1.9 months) and in five patients receiving placebo (7 events; mean duration of exposure, 4.3±2.6 months).

#### CONCLUSIONS

Our study shows that treatment with mepolizumab, an agent designed to target eosinophils, can result in corticosteroid-sparing for patients negative for *FIP1L1-PDGFR*A who have the hypereosinophilic syndrome. (ClinicalTrials.gov number, NCT00086658.)

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THE HYPEREOSINOPHILIC SYNDROME consists of several heterogeneous disorders characterized by sustained blood eosinophilia and eosinophil-related end-organ damage, with no identifiable cause, such as parasitic infection.<sup>1</sup> The objective of treatment is long-term reduction of blood and tissue eosinophil levels to prevent end-organ damage and thromboembolic events. Except for the myeloproliferative variant of the hypereosinophilic syndrome (associated with the Fip1-like 1–platelet-derived growth factor receptor  $\alpha$  fusion gene [*FIP1L1–PDGFRA*]), for which imatinib mesylate is considered first-line therapy, current management is based on long-term systemic corticosteroids.<sup>1–4</sup>

Eosinophil development from hematopoietic progenitors is regulated mainly by interleukin-5,<sup>5</sup> which has a selective role in eosinophil maturation, differentiation, mobilization, activation, and survival.<sup>5–11</sup> Since interleukin-5 appears to contribute to the pathogenesis of some phenotypes of the hypereosinophilic syndrome,<sup>12</sup> interleukin-5 inhibition is a logical therapeutic target for this disease.

Mepolizumab is a fully humanized, anti-interleukin-5 monoclonal immunoglobulin G1 antibody with a half-life of approximately 19 days; it does not fix complement.<sup>13,14</sup> By binding to free interleukin-5 with high affinity and specificity, it prevents interleukin-5 from associating with the interleukin-5 receptor  $\alpha$  chain on the surface of eosinophils and their progenitors. In preliminary studies of healthy volunteers and patients with atopy, mepolizumab had few side effects and lowered blood eosinophil levels.<sup>15–19</sup> Subsequent studies suggested that mepolizumab may have clinical value in patients with the hypereosinophilic syndrome.<sup>20–22</sup>

After these initial reports, we conducted a randomized, double-blind, placebo-controlled trial of targeted therapy for patients with the hypereosinophilic syndrome. Our aim was to evaluate the effects of mepolizumab on corticosteroid sparing and the maintenance of clinical stability in patients with disease that requires control with the use of corticosteroids.

## METHODS

### STUDY POPULATION

The study patients were 18 to 85 years of age and had the hypereosinophilic syndrome (defined as a blood eosinophil count >1500 per microliter for

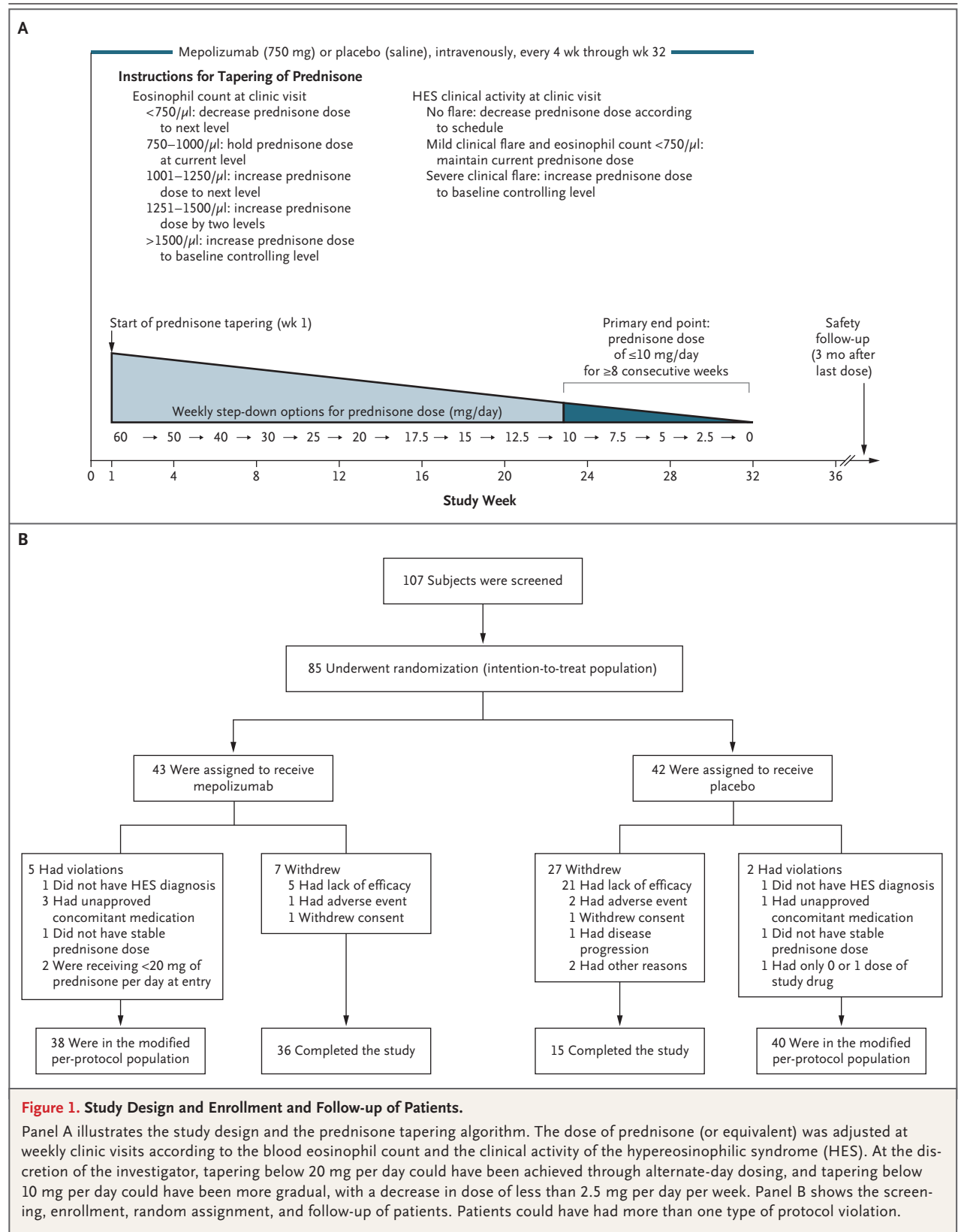
>6 months and eosinophilia-related organ involvement or dysfunction, with no identifiable secondary cause of eosinophilia<sup>23</sup>). All patients were negative for the *FIP1L1–PDGFRA* fusion gene, on the basis of in situ hybridization to detect deletion of the cysteine-rich hydrophobic domain 2 (*CHIC2*) locus, a *FIP1L1–PDGFRA* surrogate, in peripheral-blood mononuclear cells.<sup>24</sup>

### STUDY DESIGN

Our randomized, double-blind, placebo-controlled, parallel-group, multicenter study, involved 26 sites in the United States, Canada, Belgium, France, Germany, Italy, Switzerland, and Australia. It was conducted from March 2004 through March 2006. After screening, patients entered a run-in period of up to 6 weeks, during which noncorticosteroid medications for the hypereosinophilic syndrome were discontinued and prednisone monotherapy (20 to 60 mg per day for at least 1 week) was administered to achieve a stable clinical status (defined as no new or worsening clinical signs or symptoms of the hypereosinophilic syndrome and a blood eosinophil count of <1000 per microliter). Methylprednisolone, prednisolone, or triamcinolone could be used at a dose equivalent to that of prednisone, at the investigator's discretion. (See Supplementary Appendix 1, available with the full text of this article at [www.nejm.org](http://www.nejm.org), for details on blinding, exclusion criteria, eosinophil-derived neurotoxin enzyme-linked immunosorbent assay methods, and corticosteroid conversion.)

Patients whose clinical symptoms were stabilized with the use of prednisone monotherapy (20 to 60 mg per day) or the equivalent were randomly assigned in a one-to-one ratio to receive intravenous infusions of either mepolizumab (750 mg) or placebo (saline) and were stratified according to the daily prednisone dose ( $\leq 30$  mg or  $> 30$  mg) at baseline. Mepolizumab or placebo was administered every 4 weeks during a 36-week period (final infusion at week 32). The prednisone dose was tapered, starting at week 1, using a predefined algorithm based on eosinophil counts and clinical manifestations of the hypereosinophilic syndrome (Fig. 1A). Week 32 was the last visit at which a taper dose could be prescribed; the patient then took that dose until week 36, the end of the treatment period. This approach to corticosteroid dosing was used to maintain control by allowing for corticosteroid rescue therapy for disease flares.

Patients who completed the trial or withdrew



early but received at least two doses of the study drug entered an open-label extension study evaluating the long-term safety, efficacy, and optimal dosing frequency of intravenous mepolizumab. Patients choosing not to continue in the extension study completed a safety follow-up visit 3 months after their last dose of study medication.

#### CLINICAL EFFICACY

The primary end point was the reduction of the prednisone dose to 10 mg or less per day (or the equivalent) for 8 or more consecutive weeks. A prednisone dose of 10 mg or less per day was considered clinically meaningful and a response lasting 8 weeks was considered durable. All end points were analyzed with the use of data from the intention-to-treat population (85 patients who provided written informed consent, were randomly assigned to a study drug, and received at least one dose). The primary end point data were confirmed in a modified per-protocol population (78 patients). Protocol violations (by two patients in the placebo group and five in the mepolizumab group) included a lack of documented history of the hypereosinophilic syndrome, use of unapproved concomitant medications, inability to stabilize the prednisone dose within the specified range during screening, and a prednisone dose of less than 20 mg per day at study entry. Data from the patients who violated the protocol were included in the intention-to-treat analysis.

Secondary end points were a blood eosinophil count of less than 600 per microliter for 8 or more consecutive weeks, the time to treatment failure (defined as clinical worsening requiring other therapy for the hypereosinophilic syndrome, a prednisone dose of >60 mg per day, or withdrawal from the study for any reason), a prednisone dose of 7.5 mg or less per day, receipt of no prednisone for 1 day or more, the mean daily prednisone dose at week 36, and a prednisone dose of 10 mg or less per day by week 20 and for 8 or more consecutive weeks. Post hoc exploratory end points included a prednisone dose of 10 mg or less per day for 24 or more weeks and the receipt of no prednisone during the treatment period, maintained until study completion.

We assessed the effects of the study drug on physical or psychological symptoms of the hypereosinophilic syndrome, health status, and limitations of daily living, using the Medical Outcomes Study 12-item Short Form General Health Survey

(SF-12) (version 2) physical and mental component summary scores and the Rotterdam Symptom Checklist.

#### SAFETY

Safety was assessed with the use of adverse event reports, laboratory tests (clinical chemical and hematologic tests and urinalysis), electrocardiograms, physical examinations, and vital signs recorded both before and after infusion.

#### STATISTICAL ANALYSIS

We calculated that 84 patients who could be evaluated (42 per study group) would be required to provide a statistical power of 90%, at a two-sided significance level of 5%, to detect a difference of 33% between the two study groups in the percentage of patients in whom in the primary end point was reached (assuming the percentage of patients with a prednisone dose of  $\leq 10$  mg per day for  $\geq 8$  weeks was 80% in the mepolizumab group and 47% in the placebo group). Differences in the incidences of the primary end point were tested using a Cochran–Mantel–Haenszel test, with stratification according to the prednisone (or the equivalent) dose ( $\leq 30$  mg or  $>30$  mg) at baseline, at a 5% two-sided significance level in the intention-to-treat population. In the primary prespecified analysis, odds ratios were also calculated. Relative risks (without stratification on the basis of prednisone dose at baseline) and hazard ratios (with stratification) were also calculated in post-hoc analyses. The proportional-hazards assumption was assessed by inspection of the log–log survival curves.

Adverse events were also summarized. A log-rank test was used to compare the time to an adverse event between the two study groups, including data from patients who withdrew from the study.

An investigator advisory board, including the authors and the sponsor, designed the study, with scientific guidance from the Food and Drug Administration and the European Committee for Proprietary Medicinal Products. The sponsor was responsible for data collection and quality control and held the data but made them available, after ensuring confidentiality, to all the authors. All the authors analyzed and interpreted the data, wrote the manuscript, made the decision to publish, and vouch for the completeness and accuracy of the data.

**Table 1. Baseline Demographic and Disease Characteristics in the Intention-to-Treat Population.\***

Characteristic	Mepolizumab (N=43)	Placebo (N=42)	All (N=85)	P Value
Age — yr	47.0±16.2	49.1±14.4	48.1±15.3	0.52
Male sex — no. (%)	26 (60)	17 (40)	43 (51)	0.07
Race or ethnic group — no. (%)†				0.45
White	38 (88)	34 (81)	72 (85)	
Black	3 (7)	5 (12)	8 (9)	
Asian	2 (5)	1 (2)	3 (4)	
Arabic or North African	0	2 (5)	2 (2)	
Weight — kg	80.9±22.2	79.7±18.3	80.3±20.3	0.79
Body-mass index‡	27.0±6.4	27.8±5.8	27.4±6.1	0.56
Prednisone dose — no. (%)				
≤30 mg/day	30 (70)	30 (71)	60 (71)	0.87
>30 mg/day	13 (30)	12 (29)	25 (29)	
Treated for HES within past 5 yr — no. (%)	41 (95)	40 (95)	81 (95)	0.98
Most common discontinued treatments for HES — no. (%)				
Any	29 (67)	22 (52)	51 (60)	0.16
Imatinib mesylate	18 (42)	14 (33)	32 (38)	0.42
Interferon alfa	8 (19)	10 (24)	18 (21)	0.56
Hydroxyurea	9 (21)	9 (21)	18 (21)	0.96
Most common ongoing treatments for HES — no. (%)				
Any	34 (79)	36 (86)	70 (82)	0.42
Systemic corticosteroids	34 (79)	36 (86)	70 (82)	0.42
Interferon alfa	2 (5)	1 (2)	3 (4)	0.57
HES duration — yr	4.3±5.6	6.5±9.5	5.4±7.8	0.20
Age at HES onset — yr	42.7±17.7	42.7±16.2	42.7±16.9	0.99
Most prevalent HES-related current clinical condition or disorder — no. (%)§				
Any	34 (79)	36 (86)	70 (82)	0.42
Skin or subcutaneous	16 (37)	24 (57)	40 (47)	0.07
Respiratory	19 (44)	16 (38)	35 (41)	0.57
Nervous system	9 (21)	9 (21)	18 (21)	0.96
Gastrointestinal	8 (19)	7 (17)	15 (18)	0.81
Musculoskeletal	6 (14)	7 (17)	13 (15)	0.73
Cardiac	5 (12)	5 (12)	10 (12)	0.97
Eye	4 (9)	3 (7)	7 (8)	0.72
Eosinophil count				
Mean — ×10 <sup>-9</sup> /liter	0.336±0.332	0.561±0.921	0.447±0.694	0.88¶
Median — ×10 <sup>-9</sup> /liter	0.210	0.195	0.200	
Serum interleukin-5 — pg/ml	8.7, 57.0	72.0		
Serum tryptase — μg/liter***				
Mean	5.7±3.5	8.2±9.8	6.9±7.3	0.46¶
Median	5.0	6.0	5.0	

\* Plus-minus values are means ±SD. Unless otherwise stated, P values were calculated with the use of a two-sided t-test with pooled variance (for continuous data) or a chi-square test (for categorical data).

† Race or ethnic group was assessed by the investigator at screening. "Asian" consists of East, Southeast, and South Asian.

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

§ Patients may have had more than one current clinical condition or disorder related to the hypereosinophilic syndrome (HES).

¶ This P value was calculated with the use of the Wilcoxon rank-sum test.

|| Serum interleukin-5 levels for all but three patients (two in the mepolizumab group and one in the placebo group) were under the limit of detection for the assay (7.8 pg/ml). The levels for the three individual patients are reported here.

\*\*\* Serum tryptase data were available for 78 patients (41 in the mepolizumab group and 37 in the placebo group).

**Table 2.** Effects of Treatment on Corticosteroid Use and Eosinophil Counts in the Intention-to-Treat Population.\*

End Point	Mepolizumab (N=43)	Placebo (N=42)	Odds Ratio or Adjusted Mean Difference (95% CI)†‡	P Value
<b>Primary</b>				
Prednisone dose of $\leq 10$ mg/day for $\geq 8$ wk — no. (%)				
All patients	36 (84)	18 (43)	8.0 (2.7 to 23.8)	<0.001
Patients receiving prednisone dose of $\leq 30$ mg/day at baseline	26/30 (87)	17/30 (57)	5.0 (1.4 to 17.8)	0.01
Patients receiving prednisone dose of $>30$ mg/day at baseline	10/13 (77)	1/12 (8)	36.7 (3.3 to 412.3)	<0.001
<b>Secondary</b>				
Eosinophil count of $<600/\mu\text{l}$ for $\geq 8$ wk — no. (%)				
All patients	41 (95)	19 (45)	18.9 (4.7 to 75.2)	<0.001
Patients receiving prednisone dose of $\leq 30$ mg/day at baseline	28/30 (93)	18/30 (60)	9.3 (1.9 to 46.7)	0.002
Patients receiving prednisone dose of $>30$ mg/day at baseline‡	13/13 (100)	1/12 (8)		<0.001
Prednisone dose of $\leq 7.5$ mg/day for $\geq 1$ day — no. (%)				
All patients	37 (86)	21 (50)	5.5 (2.0 to 15.0)	<0.001
No prednisone for $\geq 1$ day — no. (%)				
All patients	34 (79)	10 (24)	12.8 (4.4 to 37.4)	<0.001
Prednisone dose of $\leq 10$ mg/day by wk 20 and for $\geq 8$ wk — no. (%)				
All patients	33 (77)	16 (38)	6.0 (2.2 to 16.2)	<0.001
Daily prednisone dose — mg				
At baseline	29.2 $\pm$ 1.6	30.6 $\pm$ 1.9§		
At wk 36	6.2 $\pm$ 1.9	21.8 $\pm$ 1.9	-15.7 (-20.8 to -10.6)	<0.001
SF-12 summary score¶				
Physical component				
Baseline score	42.4 $\pm$ 1.7	42.5 $\pm$ 1.6		
Adjusted change from baseline at wk 36	1.0 $\pm$ 1.6	0.4 $\pm$ 1.7	0.63 (-3.73 to 4.98)	0.78
Mental component				
Baseline score	48.3 $\pm$ 1.8	43.4 $\pm$ 1.5		
Adjusted change from baseline at wk 36	2.4 $\pm$ 1.6	0.2 $\pm$ 1.7	2.20 (-2.24 to 6.64)	0.33
<b>Exploratory</b>				
Prednisone dose of $\leq 10$ mg/day for $\geq 24$ wk — no. (%)				
All patients	24 (56)	6 (14)	7.8 (2.7 to 23.0)	<0.001
No prednisone during treatment period and until study completion — no. (%)				
All patients	20 (47)	2 (5)	17.7 (3.7 to 83.8)	<0.001

\* Plus-minus values are means  $\pm$ SE. Odds ratios and hazard ratios were adjusted for prednisone dose at baseline ( $\leq 30$  mg per day vs.  $>30$  mg per day). Hazard ratios are not reported for end points for which the assumption of proportional hazards was not fulfilled.

† The odds ratio is given for categorical variables. For the continuous variables SF-12 scores and daily dose, the adjusted mean difference was calculated, with the use of analysis of variance, and the adjusted change from baseline at week 36 was calculated with the use of last-observation-carried-forward analysis.

‡ The odds ratio for this subgroup could not be calculated because of the 100% incidence in the mepolizumab group.

§ This value is based on data from 41 patients only, since 1 patient received only one infusion.

¶ The SF-12 (version 2) physical and mental component summary scores were transformed to a mean of 50 and an SD of 10 in the general U.S. population.<sup>25</sup> Higher scores indicate a better state of health and better functioning. Scores were known for 38 patients in the mepolizumab group and 35 in the placebo group.

## RESULTS

### BASILINE CHARACTERISTICS

Of the 107 patients screened, 85 were randomly assigned to treatment with mepolizumab (43 patients) or placebo (42 patients). The majority of patients in the mepolizumab group (36 of 43 [84%])

completed the trial, as compared with only 15 of 42 (36%) in the placebo group (Fig. 1B). The most common reason for withdrawal was lack of efficacy (5 of 43 patients [12%] receiving mepolizumab and 21 of 42 [50%] receiving placebo).

There were no significant differences in demographic or disease characteristics between the

Hazard Ratio (95% CI)	P Value	Relative Risk (95% CI)	P Value
2.90 (1.59 to 5.26)	<0.001	1.95 (1.34 to 2.84)	<0.001
2.39 (1.27 to 4.50)	0.007	1.53 (1.09 to 2.16)	0.01
		9.23 (1.38 to 61.72)	<0.001
3.53 (1.94 to 6.45)	<0.001	2.11 (1.50 to 2.96)	<0.001
2.27 (1.19 to 4.33)	0.01	1.56 (1.14 to 2.12)	0.002
		12.00 (1.84 to 78.37)	<0.001
2.70 (1.56 to 4.66)	<0.001	1.72 (1.24 to 2.38)	<0.001
3.60 (1.77 to 7.30)	<0.001	3.32 (1.89 to 5.83)	<0.001
3.18 (1.70 to 5.96)	<0.001	2.01 (1.32 to 3.06)	<0.001
2.74 (1.09 to 6.90)	0.03	3.91 (1.78 to 8.58)	<0.001
		9.77 (2.43 to 39.21)	<0.001

study groups at the time of randomization (Table 1). Of note, the mean duration of disease was more than 5 years, and the majority of patients (82%) reported at least one clinical manifestation of the hypereosinophilic syndrome.

#### EFFICACY

##### *Prednisone-Sparing Effects*

Overall, for 36 patients (84%) receiving mepolizumab and 18 (43%) receiving placebo, the prednisone dose was reduced to  $\leq 10$  mg per day for  $\geq 8$  consecutive weeks during the 36-week treatment period (primary end point) (hazard ratio, 2.90; 95% confidence interval [CI], 1.59 to 5.26;  $P < 0.001$ ) (Table 2 and Fig. 2A). Similar results were obtained when the primary end point was analyzed

for the modified per-protocol population of 78 patients (hazard ratio, 3.27; 95% CI, 1.73 to 6.18;  $P < 0.001$ ). A significant difference between the two study groups was also found for the subgroups of prednisone dose at baseline, being more pronounced among patients requiring more than 30 mg per day than among those requiring 30 mg or less per day (Table 2). In the placebo group, the primary end point was more likely to be reached among patients who had been receiving 30 mg or less of prednisone at baseline (17 of 30 patients [57%]) than among those who had been receiving more than 30 mg (1 of 12 [8%]). In contrast, in the mepolizumab group, 26 of the 30 patients (87%) who had been receiving 30 mg or less of prednisone at baseline were responders, as were 10 of 13 (77%) who had been receiving more than 30 mg.

All secondary and exploratory efficacy end points significantly favored the use of mepolizumab ( $P < 0.001$ ) (Table 2 and Fig. 2B). Figure 2D shows the mean prednisone dose used during the study. (Additional efficacy analyses, with stratification on the basis of achievement of the primary end point and status of study completion, are presented in Supplementary Appendix 3.)

##### *Blood Eosinophil Counts and Eosinophil-Derived Neurotoxin Levels*

A blood eosinophil count of less than 600 per microliter for 8 or more consecutive weeks was reached in 41 of the 43 patients (95%) receiving mepolizumab, as compared with 19 of the 42 (45%) receiving placebo ( $P < 0.001$ ; hazard ratio, 3.53; 95% CI, 1.94 to 6.45) (Table 2 and Fig. 2C). The difference between the study groups for this end point was significant in both subgroups of baseline prednisone dose ( $\leq 30$  mg and  $> 30$  mg). Mean serum eosinophil-derived neurotoxin levels were significantly different between the two study groups at all time points evaluated ( $P < 0.001$ ,  $P < 0.001$ , and  $P = 0.005$  for reductions between the mepolizumab group and the placebo group at weeks 12, 24, and 36, respectively) (Fig. 2F).

##### *Time to Treatment Failure*

The time to treatment failure (defined as the number of days to clinical worsening requiring other therapy for the hypereosinophilic syndrome or an increase in the prednisone dose to  $> 60$  mg per day) was significantly shorter in the placebo group than in the mepolizumab group ( $P < 0.001$  by the log-rank test). Nine of 43 patients (21%) receiving



mepolizumab and 29 of 42 (69%) receiving placebo had treatment failure. The median time to treatment failure in the placebo group was 136.5 days (95% CI, 106 to 199; Fig. 2E); corresponding data could not be calculated for mepolizumab, since less than half the patients receiving that drug had treatment failure.

#### Health Outcomes

No significant differences between treatments were observed in the changes from baseline in SF-12 physical and mental component summary scores (Table 2) or the Rotterdam Symptom Checklist (Supplementary Appendix 3).

#### SAFETY

The mean ( $\pm$ SD) duration of exposure to study drug (defined as the time between the first and last infusions) was greater in the mepolizumab group ( $6.7\pm 1.9$  months) than in the placebo group ( $4.3\pm 2.6$  months) because of a lower withdrawal rate. Despite the longer exposure to mepolizumab, adverse events were reported at similar rates in the two study groups: 40 of 43 patients (93%) receiving mepolizumab and 41 of 42 (98%) receiving placebo (Table 3). An adverse event considered by the investigator to be related to the study drug occurred in 16 of 43 patients (37%) in the mepolizumab group and in 12 of 42 (29%) in the placebo group (Table 3). One patient receiving mepolizumab and four receiving placebo had adverse events leading to withdrawal; none of these events were considered by the investigator to be related to study drug. No clinically relevant trends or major safety concerns emerged from evaluation of the laboratory tests, vital signs, or electrocardiographic results.

Serious adverse events occurred in seven patients receiving mepolizumab (14 events, including one death) and five patients receiving placebo (7 events) (Table 3), but none were deemed by the investigator to be related to the study drug. Serious adverse events in the mepolizumab group were asthma, clinical flares of the hypereosinophilic syndrome, pneumonia, renal failure, bronchitis, cardiac arrest, dehydration, hepatitis, pancreatitis, pyrexia, rhinitis, and spinal compression fracture. Serious adverse events in the placebo group were clinical flares of the hypereosinophilic syndrome, pneumonia, dysesthesia, eosinophilia, nephrotic

#### Figure 2 (facing page). Efficacy of Mepolizumab Treatment.

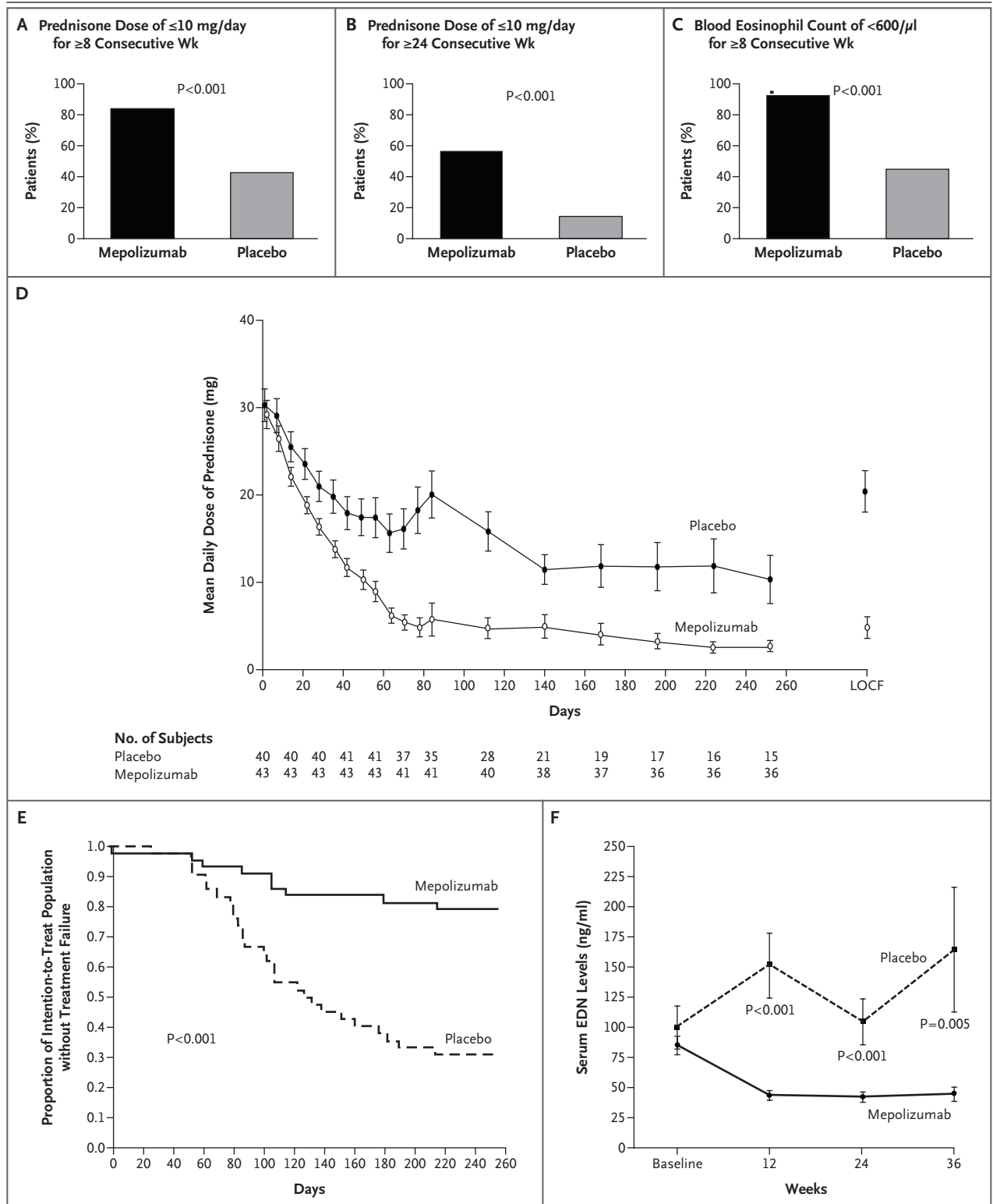
Panel A shows the percentage of patients in whom the prednisone dose was reduced to 10 mg or less per day (or the equivalent) for 8 or more consecutive weeks (the primary end point). Panel B shows the percentage of patients in whom the prednisone dose was reduced to 10 mg or less per day for 24 or more consecutive weeks. Panel C shows the percentage of patients in whom the blood eosinophil count was maintained at or below 600 per microliter for 8 or more consecutive weeks. Panel D shows the mean prednisone (or the equivalent) daily dose during the study. The last-observation-carried-forward (LOCF) data are those from the second infusion onward. Panel E is a Kaplan–Meier plot of the time to treatment failure (defined as clinical worsening requiring other therapy for the hypereosinophilic syndrome, a prednisone dose of  $>60$  mg per day, or study withdrawal for any reason) in the intention-to-treat population. Panel F shows the mean serum eosinophil-derived neurotoxin (EDN) values. The I bars in Panels D and F indicate standard errors.

syndrome, osteonecrosis, and polyneuropathy. An 18-year-old man with severe hypereosinophilic syndrome and a history of multiple cardiovascular coexisting conditions died 110 days after his first mepolizumab infusion, and 26 days after his fourth and last infusion, from a cardiac arrest attributed to dysrhythmia and internal pacemaker–defibrillator failure. (Supplementary Appendixes 2 and 4 contain additional information about adverse events.)

#### DISCUSSION

The hypereosinophilic syndrome is a potentially severe and debilitating multisystem disorder associated with considerable morbidity, in part due to the side effects of treatments currently used for it. We report evidence that corticosteroid-sparing is enabled by mepolizumab in patients negative for *FIP1L1–PDGFRA* with the hypereosinophilic syndrome. Treatment with prednisone, which could be discontinued until study completion, was able to be stopped during the study in almost 50% of patients receiving mepolizumab.

Mepolizumab also was significantly more effective than placebo at stabilizing blood eosinophil counts. These effects are clinically relevant, given that reducing eosinophil levels is currently the primary treatment goal for patients with the hypereosinophilic syndrome and that long-term



<b>Table 3. Adverse Events Reported during the 36-Week Study.*</b>		
<b>Event</b>	<b>Mepolizumab (N = 43)</b>	<b>Placebo (N = 42)</b>
	<i>number of patients (percent)</i>	
<b>Serious adverse event</b>		
Any	7 (16)	5 (12)
Asthma	2 (5)	0
Hypereosinophilic syndrome flare	1 (2)	1 (2)
Pneumonia	1 (2)	1 (2)
Renal failure	2 (5)	0
Bronchitis	1 (2)	0
Cardiac arrest	1 (2)	0
Dehydration	1 (2)	0
Dysesthesia	0	1 (2)
Eosinophilia	0	1 (2)
Hepatitis	1 (2)	0
Nephrotic syndrome	0	1 (2)
Osteonecrosis	0	1 (2)
Pancreatitis	1 (2)	0
Polyneuropathy	0	1 (2)
Pyrexia	1 (2)	0
Rhinitis resulting in hospital admission	1 (2)	0
Spinal compression fracture	1 (2)	0
<b>Adverse event</b>		
Any event	40 (93)	41 (98)
Fatigue	13 (30)	11 (26)
Pruritus	12 (28)	9 (21)
Headache	10 (23)	9 (21)
Arthralgia	9 (21)	7 (17)
Nausea	8 (19)	7 (17)
Diarrhea	8 (19)	6 (14)
Cough	5 (12)	8 (19)
Dyspnea	7 (16)	6 (14)
Upper respiratory tract infection	9 (21)	4 (10)
Back pain	5 (12)	6 (14)
Myalgia	8 (19)	3 (7)
Peripheral edema	7 (16)	4 (10)
Sinusitis	5 (12)	6 (14)
Rash	4 (9)	6 (14)
Abdominal pain	4 (9)	5 (12)
Pyrexia	3 (7)	6 (14)
Vomiting	5 (12)	4 (10)
Asthma	5 (12)	3 (7)
Dizziness	5 (12)	3 (7)

**Table 3. (Continued.)**

Event	Mepolizumab (N=43)	Placebo (N=42)
	<i>number of patients (percent)</i>	
Nasopharyngitis	4 (9)	4 (10)
Rhinitis	6 (14)	2 (5)
Pharyngolaryngeal pain†	1 (2)	6 (14)
Bronchitis	5 (12)	1 (2)
Chest pain	4 (9)	2 (5)
Clinically significant or unexpected worsening of HES	2 (5)	4 (10)
Pain in extremity‡	1 (2)	5 (12)
Paresthesia	3 (7)	3 (7)
Urticaria	5 (12)	1 (2)
Acne	3 (7)	2 (5)
Contusion	2 (5)	3 (7)
Erythema	3 (7)	2 (5)
Muscle spasms	3 (7)	2 (5)
Facial swelling	2 (5)	3 (7)
Neck pain	1 (2)	3 (7)
Papular rash	1 (2)	3 (7)
Allergic rhinitis	4 (9)	0
Urinary tract infection	1 (2)	3 (7)
Alopecia	3 (7)	0
Epistaxis	3 (7)	0
Productive cough	3 (7)	0
<b>Drug-related adverse event</b>		
Any event	16 (37)	12 (29)
Headache	2 (5)	4 (10)
Arthralgia	4 (9)	2 (5)
Fatigue	4 (9)	1 (2)
Peripheral edema	0	4 (10)
Pruritus	2 (5)	2 (5)
Myalgia	2 (5)	2 (5)
Erythema	1 (2)	2 (5)
Rash	1 (2)	2 (5)
Increased $\gamma$ -glutamyltransferase	2 (5)	0
Cough	0	3 (7)
Dyspnea	0	2 (5)

\* Some patients had more than one adverse event. The serious adverse events and adverse events listed were those reported at an incidence of more than 5% per study group. The drug-related adverse events listed (those considered to be such by the investigator) were those reported at an incidence of more than 4% per study group. No statistical testing was performed on data for drug-related adverse events. For serious adverse events and adverse events, all comparisons were not significant, unless otherwise noted. HES denotes the hypereosinophilic syndrome.

† P=0.03 for the comparison of the mepolizumab group and the placebo group.

‡ P=0.047 for the comparison of the mepolizumab group and the placebo group.

corticosteroid therapy is associated with a range of undesirable side effects.<sup>26-28</sup> Since the corticosteroid threshold associated with clinically significant toxic effects has been established at approximately 7.5 mg per day of prednisone equivalent,<sup>27</sup> it is notable that a prednisone dose of 7.5 mg or less per day in this study was achieved in significantly more patients receiving mepolizumab than in those receiving placebo.

No significant differences were found between the two study groups in SF-12 (version 2) assessments, which may reflect the protocol requirements for disease to be clinically stable at baseline and for stability to be maintained in order for the patient to remain in the trial. As such, the quality of life, as measured by the SF-12 survey, did not deteriorate during the study period. In addition, the baseline mental-component summary score in the mepolizumab group was similar to that for the general U.S. population,<sup>25</sup> indicating that with treatment, patients did not feel impaired by their disease, making it difficult to show an improvement. The study population was composed of relatively young patients who were negative for *FIP1L1-PDGFR*A and had long-standing corticosteroid-responsive hypereosinophilic syndrome. The corticosteroid-sparing effects observed in our study suggest that mepolizumab has substantial potential to reduce treatment-related morbidity. Because this study was limited to patients who were receiving corticosteroid therapy and whose hypereosinophilic syndrome was clinically well controlled, no recommendations can be inferred regarding the use of mepolizumab for patients with acute presentations or who have not yet received corticosteroid therapy. The same holds true for patients with the hypereosinophilic syndrome that is unresponsive to systemic corticosteroids, as well as those positive for *FIP1L1-PDGFR*A.<sup>29</sup>

Mean serum interleukin-5 values at baseline were below the limit of detection (7.8 pg per milliliter) in most patients (Table 1). Such normal serum interleukin-5 levels are probably due to corticosteroid-induced suppression, since patients' symptoms were stabilized by means of corticosteroid therapy before randomization. The efficacy of mepolizumab in patients with physiologic levels of interleukin-5 suggests that this agent should not be reserved for patients with elevated serum interleukin-5 levels. Our results provide evidence that endogenous interleukin-5 in these patients

with the hypereosinophilic syndrome has a critical role in regulating peripheral eosinophilia.

Our study assessed the effects of mepolizumab administered monthly during a 36-week treatment period, whereas previous studies of mepolizumab evaluated 12 weeks of treatment.<sup>15,17,18,22,30</sup> Several of these studies focused on the treatment of asthma, showing significant reductions in blood, sputum, and bronchial eosinophil counts and safety but limited efficacy as measured by pulmonary-function testing.<sup>15-18</sup> Much remains to be learned about the relation between blood and tissue eosinophilia and clinical response to treatment in patients with asthma and the hypereosinophilic syndrome. Although the number of patients in our trial was small, the preliminary findings suggest that the likelihood of achieving the primary end point with the use of mepolizumab was high in the patients with current conditions related to the hypereosinophilic syndrome. The primary end point was reached in 17 of the 19 patients with respiratory disorders, 5 of the 5 with cardiac disorders, 8 of the 8 with gastrointestinal disorders, 5 of the 6 with musculoskeletal disorders, and 8 of the 9 with nervous-system disorders, although in only 11 of the 16 patients with skin or subcutaneous manifestations (Table 1, and Supplementary Appendix 5).

In theory, since interleukin-5 potently primes eosinophils for enhanced responsiveness to activating signals,<sup>6</sup> anti-interleukin-5 may be particularly helpful for reducing the eosinophil-mediated end-organ pathologic characteristics typically associated with the hypereosinophilic syndrome. Tissue and vascular damage results in part from the release of granule proteins, and mepolizumab treatment was associated with significant reductions in eosinophil-derived neurotoxin levels in our study (Fig. 2F). In addition, the chronic tissue damage associated with the hypereosinophilic syndrome is thought to be mediated by eosinophil infiltration, and mepolizumab probably decreases tissue eosinophil levels in patients with the syndrome.<sup>21,22</sup>

Adverse effects were found in the mepolizumab group. One patient receiving mepolizumab had a fatal cardiac arrest, which was not considered to be drug-related by the investigator, who was unaware of the group assignment. Adverse events considered drug-related by the investigator were similar between the mepolizumab group and the

placebo group. This finding is noteworthy, since the duration of exposure to study drug was approximately 56% longer for mepolizumab than for placebo, owing to the greater dropout rate (because of lack of efficacy) in the placebo group. In addition, some adverse events in both groups may have resulted from prednisone withdrawal rather than use of the study drug.

An ongoing, open-label extension trial, involving 78 patients from the current trial, will provide long-term information on potential safety issues, efficacy assessments, and optimal dosing frequency (see Supplementary Appendix 4 for details). This trial will help address whether long-term treatment with mepolizumab will durably reduce eosinophil counts while controlling disease.

In conclusion, our study demonstrated that mepolizumab treatment enabled clinically significant reductions in corticosteroid dose, and often corticosteroid discontinuation, in patients negative for *FIP1L1-PDGFR* who had the hypereosinophilic syndrome. This proof-of-concept study shows that administration of anti-interleukin-5 antibodies, an eosinophil-specific and targeted therapy, has a potential clinical benefit.

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#### APPENDIX

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#### REFERENCES

- Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol* 2006; 117:1292-302.
- Gleich GJ, Leiferman KM. The hypereosinophilic syndromes: still more heterogeneity. *Curr Opin Immunol* 2005;17:679-84.
- Roufosse F, Goldman M, Cogan E. Hypereosinophilic syndrome: lymphoproliferative and myeloproliferative variants. *Semin Respir Crit Care Med* 2006;27:158-70.
- Wilkins HJ, Crane MM, Copeland K, Williams WV. Hypereosinophilic syndrome: an update. *Am J Hematol* 2005;80: 148-57.
- Kariyawasam HH, Robinson DS. The eosinophil: the cell and its weapons, the cytokines, its locations. *Semin Respir Crit Care Med* 2006;27:117-27.
- Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006;24:147-74.
- Lopez AF, Sanderson CJ, Gamble JR, Campbell HD, Young IG, Vadas MA. Recombinant human interleukin 5 is a selective activator of human eosinophil function. *J Exp Med* 1988;167:219-24.
- Clutterbuck EJ, Hirst EM, Sanderson CJ. Human interleukin-5 (IL-5) regulates the production of eosinophils in human bone marrow cultures: comparison and interaction with IL-1, IL-3, IL-6, and GM-CSF. *Blood* 1989;73:1504-12.
- Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood* 1992;79:3101-9.
- Simon D, Braathen LR, Simon H-U. Eosinophils and atopic dermatitis. *Allergy* 2004;59:561-70.
- Sutton SA, Assa'ad AH, Rothenberg ME. Anti-IL-5 and hypereosinophilic syndromes. *Clin Immunol* 2005;115:51-60.

12. Schrezenmeier H, Thomé SD, Tewald F, Fleischer B, Raghavachar A. Interleukin-5 is the predominant eosinophilopoietin produced by cloned T lymphocytes in hypereosinophilic syndrome. *Exp Hematol* 1993;21:358-65.
13. Cook R, Applebaum R, Cusimano D, et al. Biological and biophysical characteristics of SB 240563, a high affinity humanized monoclonal antibody to IL-5. *Am J Crit Care Med* 1998;157:A604. abstract.
14. Hart TK, Cook RM, Zia-Amirhosseini P, et al. Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys. *J Allergy Clin Immunol* 2001;108:250-7.
15. Büttner C, Lun A, Spletstoesser T, Kunkel G, Renz H. Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell functions. *Eur Respir J* 2003; 21:799-803.
16. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356:2144-8.
17. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167:199-204.
18. Menzies-Gow A, Flood-Page P, Sehmi R, et al. Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. *J Allergy Clin Immunol* 2003;111:714-9.
19. Oldhoff JM, Darsow U, Werfel T, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* 2005;60:693-6.
20. Koury MJ, Newman JH, Murray JJ. Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib. *Am J Med* 2003;115: 587-9.
21. Plötz SG, Simon H-U, Darsow U, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003; 349:2334-9.
22. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004;113:115-9.
23. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore)* 1975; 54:1-27.
24. Pardanani A, Ketterling RP, Brockman SR, et al. CHIC2 deletion, a surrogate for FIP1L1-PDGFR $\alpha$  fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. *Blood* 2003;102: 3093-6.
25. Ware JE, Kosinski M, Keller SD. SF-12: how to score the SF-12 Physical and Mental Health Summary Scales. Boston: The Health Institute, New England Medical Center, 1995.
26. Stanbury RM, Graham EM. Systemic corticosteroid therapy — side effects and their management. *Br J Ophthalmol* 1998; 82:704-8.
27. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* 2004;141:764-70.
28. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids — new mechanisms for old drugs. *N Engl J Med* 2005;353:1711-23.
29. Klion AD, Law MA, Noel P, Kim YJ, Haverty TP, Nutman TB. Safety and efficacy of the monoclonal anti-interleukin-5 antibody SCH55700 in the treatment of patients with hypereosinophilic syndrome. *Blood* 2004;103:2939-41.
30. Phipps S, Flood-Page P, Menzies-Gow A, Ong YE, Kay AB. Intravenous anti-IL-5 monoclonal antibody reduces eosinophils and tenascin deposition in allergen-challenged human atopic skin. *J Invest Dermatol* 2004;122:1406-12.

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