

A review of treatment with mepolizumab, an anti-IL-5 mAb, in hypereosinophilic syndromes and asthma

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The hypereosinophilic syndromes (HESs) are a heterogeneous group of diseases characterized by peripheral blood eosinophilia with end-organ damage and varying in severity from nonspecific symptoms to life-threatening. Treatment objectives are a safe reduction of blood and tissue eosinophil levels and prevention of eosinophil-mediated tissue damage. Current treatment of patients with HESs, who lack the FIP-1-like 1-platelet-derived growth factor receptor α (*FIP1L1-PDGFR α*) fusion gene, is mainly systemic corticosteroid therapy. Eosinophil development from hematopoietic progenitor cells is regulated by IL-5, which influences maturation, differentiation, mobilization, activation, and survival. Consequently, inhibiting IL-5 is a logical therapeutic objective for patients with HESs or selected patients with asthma. Mepolizumab is a fully humanized anti-IL-5 monoclonal IgG₁ antibody that binds to free IL-5 with high affinity and specificity to prevent IL-5 from associating with the IL-5 receptor complex α -chain on the surface of eosinophils. In clinical trials with patients with HESs, mepolizumab reduced

blood eosinophil counts and the maintenance corticosteroid dose and had no major safety concerns. Mepolizumab reduced airway and blood eosinophils and prevented asthma exacerbations. Thus, mepolizumab may be effective for long-term treatment of patients with selected eosinophilic disorders. (J Allergy Clin Immunol 2010;125:803-13.)

Key words: Anti-IL-5, hypereosinophilic syndrome, IL-5, mepolizumab

Eosinophils are involved in the initiation and propagation of diverse inflammatory responses. Eosinophils are recruited from the circulation to sites of inflammation, where they affect the immune response through a variety of mechanisms, including antigen presentation and release of proinflammatory cytokines, chemokines, lipid mediators, and cytotoxic granules (Fig 1).¹ Under normal conditions, most eosinophils reside in the gastrointestinal tract, where they are believed to participate in host defense against helminth parasites.² Tissue damage and dysfunction may follow secretion of these cell's pleiotropic mediators, thus leading to eosinophil-driven diseases, including hypereosinophilic syndromes (HESs).

IL-3, IL-5, and GM-CSF regulate eosinophil development. Of these, IL-5 is most specific to eosinophils and is the major hematopoietin responsible for eosinophil growth, differentiation, mobilization, recruitment, activation, and survival.³⁻⁶ IL-5 acts through the IL-5 receptor complex expressed on the eosinophil cell surface. The α -chain of the receptor is specific for IL-5; the β -chain is the signal-transducing unit. IL-5 receptors are also present on human basophils,⁷ and IL-5 can modulate basophil function, especially with regard to histamine release.^{8,9}

HES

The HESs are a group of rare hematologic disorders that are often characterized by a blood eosinophil count of $>1500/\mu\text{L}$ for more than 6 months, evidence of end-organ involvement with eosinophil infiltration and injury, and no identifiable cause (such as parasitic infection, allergy, or hematologic malignancy).^{10,11} Clinical manifestations of the syndrome vary extensively from nonspecific symptoms to multiple end-organ damage or dysfunction resulting from eosinophilic infiltration and local release of proinflammatory mediators and toxic granule products.¹² The organs most frequently affected are the heart, lungs, liver, nervous system, skin, and digestive tract.¹³⁻¹⁵ Cardiac involvement is the major cause of morbidity and mortality.¹³

Accurate diagnosis and better management of end-organ damage has improved the prognosis of patients with HESs.^{16,17}

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Abbreviation usedFIPIL1-PDGFR α : FIP-1-like 1-platelet-derived growth factor receptor α

HES: Hypereosinophilic syndrome

Clinical HES subtypes include lymphocytic-variant and myeloproliferative-variant HES, or the disease may be classified as “undefined.”^{11,18,19} Eosinophilia in patients with lymphocytic-variant HES has been attributed to a high expression of eosinophilopoietic cytokines, including IL-5, from a clonal T-cell population with an aberrant surface phenotype (eg, CD3⁺CD4⁺ or CD3⁺CD4⁺CD8⁺).¹⁹⁻²³ In comparison, myeloproliferative variants are myeloid clonal disorders and may be associated with a specific cytogenetic abnormality.¹⁹ For example, fusion of the Fip1-like 1 (*FIPIL1*) gene to the platelet-derived growth factor receptor α (*PDGFR α*) gene, generated by an interstitial deletion on chromosome 4q12, has been detected in a variable proportion of patients with myeloproliferative-variant HES.²⁴ The resulting gene encodes a fusion protein (*FIPIL1-PDGFR α*) with constitutive tyrosine kinase activity, which has a central role in disease pathogenesis.^{25,26}

TREATMENT OF HESs

The primary goals of HES therapy are to reduce or minimize eosinophil-mediated end-organ damage as safely as possible. There is no single approach to treatment because of the heterogeneity in clinical presentation, end-organ involvement, and physiopathology. Consequently, selection of an appropriate therapeutic strategy should be tailored to the individual patient.^{11,27-29}

Systemic corticosteroids, such as prednisone, remain first-line therapy for the management of clinical manifestations in *FIPIL1-PDGFR α* -negative patients with symptomatic HESs.^{11,18,19,27,29} Second-line therapies for patients unresponsive to corticosteroids or intolerant of the doses required to maintain disease control include cytotoxic drugs (eg, hydroxyurea or vincristine) and IFN- α .^{11,29} Chronic use of these therapies, however, is associated with significant limitations, including toxicity, serious adverse effects, poor long-term tolerability, the development of resistance (in which case the disease may become life-threatening), and inconsistent efficacy.

Imatinib mesylate is a small molecule inhibitor of tyrosine kinases, including *FIPIL1-PDGFR α* . Targeted therapy with imatinib has proven effective in patients harboring the *FIPIL1-PDGFR α* fusion gene,^{30,31} and it is considered first-line treatment for *FIPIL1-PDGFR α* -positive patients (corticosteroids do not typically produce a response in such patients and should, therefore, not be given first-line).^{29,32} Imatinib is rarely effective in *FIPIL1-PDGFR α* -negative patients for whom alternative therapies are needed.³³⁻³⁵

Inhibition of IL-5 represents another logical targeted therapy in HESs (or other eosinophil-driven diseases), given the critical and selective role of IL-5 in eosinophil proliferation and terminal differentiation. Moreover, clonal expansion of IL-5-secreting T-cell populations (CD3⁺CD4⁺) in patients with the lymphocytic variant of HES leads to an overproduction of IL-5. Strategies aimed at antagonizing IL-5 can be expected to attenuate eosinophil maturation and trafficking into target tissues and to inhibit associated adverse sequelae without affecting the normal function

of other cells of the immune system.^{36,37} Humanized mAbs designed to inhibit human IL-5 have been developed (notably, mepolizumab and reslizumab). In a humanized antibody, the complementarity determining regions from the parent rodent antibody are grafted to the framework region of a human antibody to reduce immunogenicity. Reslizumab is a humanized rat-derived monoclonal antihuman IL-5 antibody of the IgG₄/ κ subtype,^{38,39} and mepolizumab is a humanized mouse monoclonal antihuman IL-5 antibody of the IgG₁/ κ subtype.^{40,41} The remainder of this review focuses on the safety and efficacy of mepolizumab in patients with HESs.

STUDIES OF MEPOLIZUMAB IN HESs

Case reports

The first publication on the clinical use of mepolizumab was by Koury et al⁴² (Table I). They described the case of a 51-year-old man with a 4-year history of HESs and a 5-year history of lymphomatoid papulosis. Treatment with 3 intravenous doses of mepolizumab 750 mg over a period of 6 weeks produced transient improvements in eosinophil count and symptoms, although rebound occurred within days of each dose. Subsequent treatment with imatinib mesylate produced a more sustained response. Rebound eosinophilia has also been observed in patients with HESs receiving reslizumab.^{39,43}

More encouraging results with mepolizumab were observed in a series of 3 women with *FIPIL1-PDGFR α* -negative HES and dermatologic manifestations (Table I).⁴⁴ Each initially received 2 doses of intravenous mepolizumab 750 mg, administered 2 weeks apart. Peripheral blood eosinophilia and serum eosinophilic cationic protein levels decreased within 24 hours of the first dose of mepolizumab. Skin lesions and pruritus also improved considerably within weeks of treatment initiation, and biopsy specimens showed fewer, but persistent, eosinophils in the dermis. Symptoms were controlled over the long term, either without any further therapy or with monthly doses of mepolizumab.

Open-label study of mepolizumab in HESs

A small, open-label study evaluated mepolizumab in 3 patients with HESs (Table I).⁴⁵ Antieosinophil therapy was reduced during an 8-week run-in period until blood eosinophil levels were twice initial levels or the absolute count was >750 cells/ μ L. Each patient then received 3 doses of intravenous mepolizumab 10 mg/kg (maximum, 750 mg) at intervals of 4 weeks. Follow-up assessments were conducted at 4 and 12 weeks after the final dose.

Patient 1 was a 48-year-old woman with a 10-year history of idiopathic HES with pulmonary, gastrointestinal, and skin manifestations. Clinical exacerbation during the pretreatment run-in period necessitated an increase in antieosinophil therapy, which reduced the peak eosinophil level to 300 cells/ μ L. Her baseline medication included methylprednisolone 8 mg/d and methotrexate 17.5 mg/wk. Patient 2 was a 55-year-old man with a 2-year history of idiopathic HES manifested as eosinophilic pneumonia, cellulitis, and sinusitis/nasal polyposis. He was controlled with prednisone 10 mg plus hydroxyurea 1 g daily. Patient 3, a 40-year-old woman, had a 2-year history of idiopathic HES with cardiomyopathy and asthma. Her medication at baseline was prednisone 5 mg/d.

Pronounced decreases in peripheral eosinophil counts were observed after mepolizumab administration in all 3 patients and were maintained for the duration of the study (Fig 2).

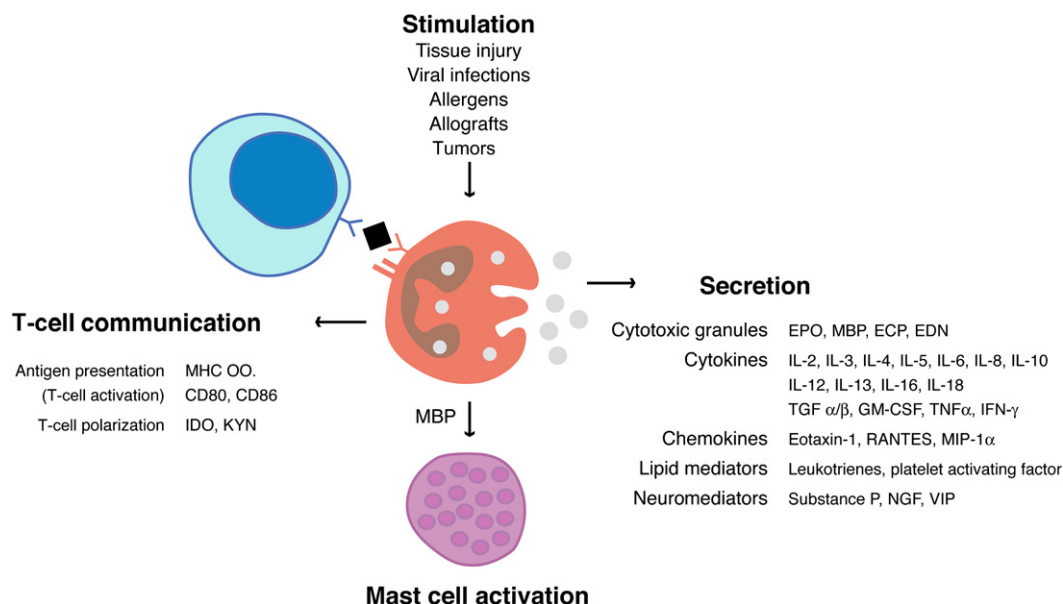


FIG 1. Schematic diagram of an eosinophil and its multifunctional effects. Eosinophils are bilobed granulocytes with eosinophilic-staining secondary granules, which contain 4 primary cationic proteins, designated eosinophil peroxidase (EPO), major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). All 4 proteins are cytotoxic molecules; in addition, ECP and EDN are ribonucleases. Eosinophils respond to diverse stimuli, including nonspecific tissue injury, viral infections, allografts, allergens, and tumors. In addition to releasing their preformed cationic proteins, eosinophils can release a variety of cytokines, chemokines, lipid mediators, and neuromodulators. Eosinophils directly communicate with T cells and mast cells in a bidirectional manner. Eosinophils activate T cells by serving as antigen-presenting cells, and eosinophil-derived MBP is a mast cell secretagogue. Eosinophils can also regulate T-cell polarization through synthesis of indoleamine 2,3-dioxygenase (IDO), an enzyme involved in oxidative metabolism of tryptophan, catalyzing the conversion of tryptophan to kynurenines (KYN), a regulator of T_H1/T_H2 balance. MIP, Macrophage inflammatory protein; NGF, nerve growth factor; VIP, vaso-intestinal peptide. From Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006;24:147-74.¹

Improvements were also observed in a variety of clinical manifestations of HESs, including pruritus, cutaneous lesions, nasal congestion, polyposis, constitutional symptoms, exercise tolerance, and FEV₁, as well as quality of life parameters.

Thus, preliminary clinical experience in patients with HESs indicated that mepolizumab treatment reduced blood eosinophils, provided variable symptom relief, and was well tolerated.

Pivotal clinical trial

On the basis of these encouraging findings, a multicenter (26 sites internationally), double-blind, randomized, placebo-controlled, parallel-group clinical trial was conducted to evaluate mepolizumab further as a therapeutic option for HESs (study MHE100185).⁴⁶ The trial involved 85 *FIP1L1-PDGFR α* -negative patients with HESs, 18 to 85 years of age, who required prednisone monotherapy of 20 to 60 mg (or equivalent) to maintain a stable clinical status and a peripheral eosinophil count of <1000 cells/ μ L. The objective was to evaluate the potential of mepolizumab to reduce corticosteroid requirements while maintaining clinical stability in patients with corticosteroid-controlled HESs. The safety and tolerability of this anti-IL-5 mAb was also assessed.

Participants received intravenous mepolizumab 750 mg (n = 43) or placebo (n = 42) every 4 weeks over a 36-week treatment period while the prednisone dose was tapered by using a predefined algorithm based on eosinophil counts and HES clinical

manifestations. Compared with placebo, mepolizumab had a greater corticosteroid-sparing capacity and was more effective at reducing eosinophil counts. Significantly more patients receiving mepolizumab than placebo achieved the primary endpoint of a prednisone dose of ≤ 10 mg/kg for at least 8 consecutive weeks (84% vs 43%; $P < .001$; odds ratio, 8.0; 95% CI, 2.7-23.8; Fig 3, A). In addition, almost 50% of mepolizumab-treated patients became corticosteroid-free during the treatment period and remained so until study completion (vs 5% of placebo-treated patients; $P < .001$; odds ratio, 17.7; 95% CI, 3.7-83.8). All other secondary and exploratory corticosteroid-sparing endpoints significantly favored the use of mepolizumab over placebo ($P < .001$). Mepolizumab also led to a pronounced reduction in blood eosinophil levels, with 95% of patients having a count of <600 eosinophils/ μ L for ≥ 8 consecutive weeks (vs 45% on placebo; $P < .001$; odds ratio, 18.9; 95% CI, 4.7-75.2; Fig 3, B). This was accompanied by a significant reduction in serum levels of eosinophil-derived neurotoxin, a cytotoxic eosinophil granule protein.

Overall adverse event rates were similar in the 2 treatment arms (93% with mepolizumab and 98% with placebo), as were treatment-related adverse event rates (37% and 29%, respectively). This was despite a greater mean ($\pm$ SD) exposure to mepolizumab (6.7 ± 1.9 months) than placebo (4.3 ± 2.6 months) resulting from a lower withdrawal rate in the mepolizumab group. Serious adverse events were reported in 7 patients treated with mepolizumab and in 5 treated with placebo. In addition, an 18-year-old man with severe HES and multiple

TABLE I. Summary of mepolizumab clinical experience in patients with the hypereosinophilic syndrome

Reference	Design	Subjects	Treatment	Results
Koury et al ⁴²	Case report	51-year-old man with a 4-year history of HESs (2,000-8,000 eosinophils/ μ L blood) and a 5-year history of lymphomatoid papulosis. Markedly elevated serum IL-5 levels	Three doses of mepolizumab 750 mg IV over 6 wk (on days 0, 14, and 43)	Transient effects (rebound within days of each dose): ● Decrease in IL-5 level and eosinophil count ● Partial improvement in pulmonary symptoms ● Elimination of lymphomatoid papulosis Subsequent treatment with imatinib mesylate produced a more sustained response
Plötz et al ⁴⁴	Case reports	Patients with HESs and eosinophilic dermatitis (all women, 60-82 years of age)	Patient 1: 2 doses of mepolizumab 750 mg IV (2 wk between doses)	Patient 1: ● Blood eosinophil count and serum ECP decreased within 1 d ● Pruritus and skin lesions resolved completely by 3 d ● Asymptomatic for 17 mo without corticosteroid or other therapy
		n = 3	Patient 2: 3 doses of mepolizumab 750 mg IV (2 wk between doses 1 and 2, and 5 wk between doses 2 and 3); monthly dosing for 7 mo	Patient 2: ● Blood eosinophil count and serum ECP decreased within 1 d ● Pruritus and other symptoms almost resolved after 3 wk ● Considerable improvement in fever, fatigue, and abdominal pain ● Monthly dosing with mepolizumab 750 mg IV prevented rebound
			Patient 3: 4 doses of mepolizumab 750 mg IV (2 wk between doses 1 and 2, 5 wk between doses 2 and 3, and 7 wk between doses 3 and 4); thereafter, monthly dosing for 5 mo	Patient 3: ● Blood eosinophil count and serum ECP decreased within 1 d ● Skin lesions regressed and the pruritus decreased within 2 wk ● Treatment was stopped because of the improvement in disease, and the patient remained almost symptom-free No adverse events were reported in any of the patients
Garrett et al ⁴⁵	Open-label	Patients with HESs (blood eosinophil count 2-fold entry level, or >750 eosinophils/ μ L of blood after an 8-wk pretreatment run-in period) 18-65 years of age n = 3	Three doses of mepolizumab 10 mg/kg (750 mg maximum) IV at 4-wk intervals	Blood eosinophil count: ● Reduced in all patients and sustained for 12 wk after the last dose Symptoms and quality of life: ● Progressive improvements in all patients FEV ₁ : ● Improved in all patients

ECP, Eosinophilic cationic protein; IV, intravenous.

coexisting cardiovascular conditions in the mepolizumab group died from a cardiac arrest attributed to dysrhythmia and internal pacemaker-defibrillator failure. None of the serious adverse events, including the death, were considered related to the study drug by the investigator. Laboratory tests, vital signs, and electrocardiographic results also raised no major safety concerns. Five patients, including 1 placebo-treated patient, tested positive for antimepolizumab antibodies, although it is unclear whether these were neutralizing antibodies. The presence of antimepolizumab antibodies was not associated with any apparent clinical or pharmacokinetic consequences.

Thus, this study showed a potential clinical benefit of mepolizumab, an eosinophil-specific and targeted therapy, in *FIP1L1-PDGFR α* -negative patients with HESs. This anti-IL-5 mAb enabled clinically meaningful corticosteroid dose reductions (and often corticosteroid withdrawal) and significantly decreased peripheral eosinophil levels, a primary treatment goal for patients with HESs.

Open-label extension study

Patients who completed the pivotal trial or withdrew early entered an open-label extension study (study MHE100901), the primary objective of which was to evaluate the long-term safety of mepolizumab in HESs. A 3-stage treatment plan was used:

- Stage 1: HES medication taper and stabilization period (subjects completing the pivotal trial on >10 mg/d prednisone entered at this stage)
- Stage 2: optimization of dosing frequency (subjects completing the pivotal trial on $\leq$ 10 mg/d prednisone entered at this stage)
- Stage 3: long-term safety and efficacy assessment

Intravenous mepolizumab 750 mg was administered monthly in stage 1, at intervals based on blood eosinophil counts and HES clinical activity in stage 2, and at an individualized dosing frequency in stage 3 (as determined in stage 2). An interim analysis was conducted on clinical data on September 3, 2007. In

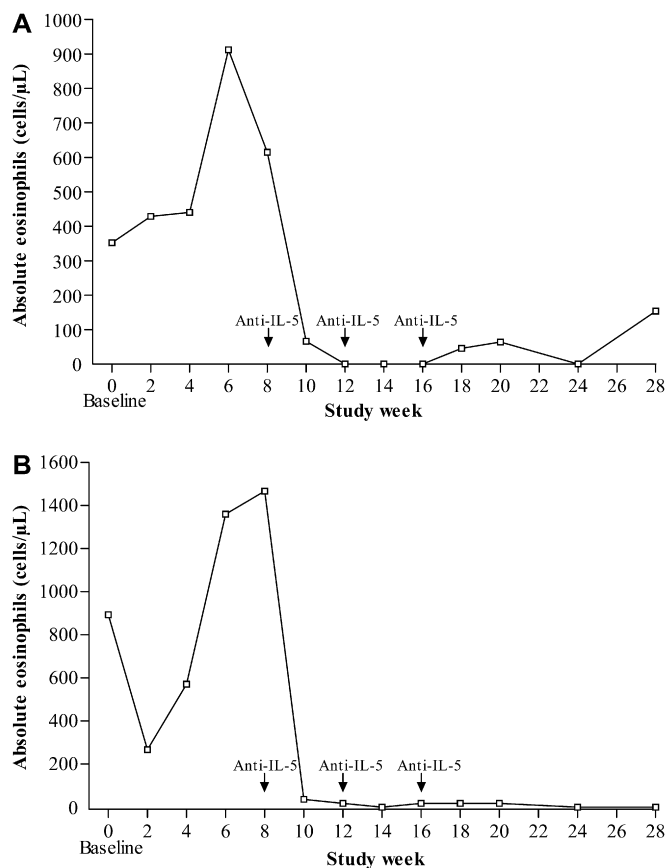


FIG 2. A and B, Eosinophil blood counts in 2 patients with HESs treated with 3 intravenous doses of mepolizumab 10 mg/kg (750 mg maximum) at intervals of 4 weeks (anti-IL-5 = mepolizumab). From Garrett JK, Jameson SC, Thomson B, Collins MH, Wagoner LE, Freese DK, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004;113:115-9.⁴⁵

addition, serious adverse event data were collected up to April 30, 2008.

Of 78 patients enrolled, 61 remained in the extension study at the time of the interim analysis. Mean exposure to mepolizumab among these patients was 20.6 months (range, 1-35 months), with a mean of 11 infusions per patient (range, 1-34). The majority of patients received infusions at intervals of 5 to 16 weeks during stage 3 of the study, when dosing frequency was individualized. This indicates that mepolizumab, like most other anticytokine antibodies (eg, anti-TNF antibodies), has a time-limited effect. An increase of eosinophils a few weeks to months after the infusion suggests the need for retreatment.

Overall, 96% of patients reported at least 1 adverse event, the most common being fatigue (26%), upper respiratory tract infection (26%), cough (23%), headache (19%), dyspnea (18%), and nausea (18%). Drug-related adverse events occurred in 22% of patients, with only fatigue, nausea, and headache reported in ≥ 2 individuals. Twenty-eight patients had nonfatal serious adverse events (total of 64 events), although there was no preponderance of any 1 type of event. Of 3 deaths, only 1 was considered possibly related to treatment (severe angioimmunoblastic T-cell lymphoma and cardiopulmonary failure in a 46-year-old man). Three patients experienced mild or moderate hypersensitivity reactions, but none of these were deemed by the

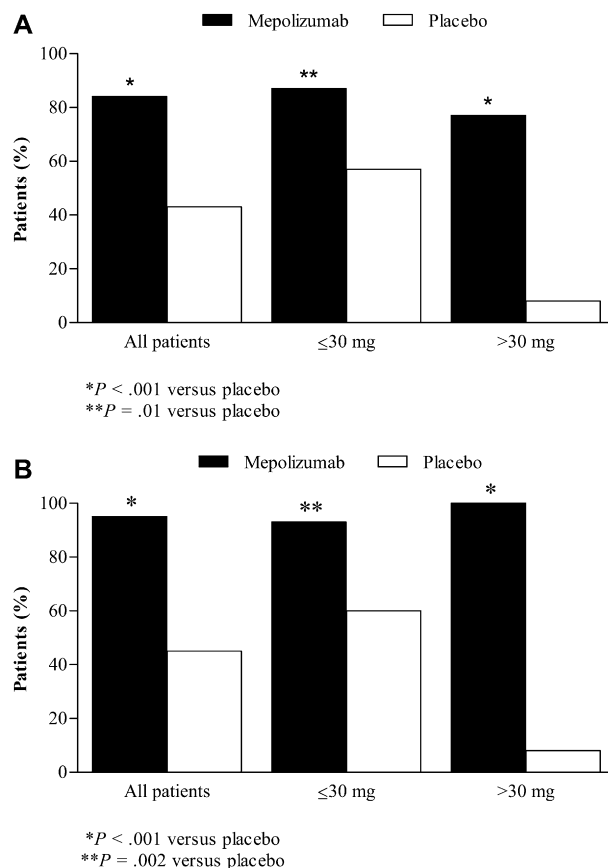


FIG 3. Effects of mepolizumab 750 mg on corticosteroid requirements and blood eosinophil counts in patients with HESs in the pivotal double-blind, randomized, placebo-controlled trial. Results are shown for the overall population and according to the daily prednisone dose at baseline (≤ 30 mg or >30 mg). **A**, Percentage of patients achieving a prednisone dose of ≤ 10 mg/d for ≥ 8 consecutive weeks (primary endpoint). **B**, Percentage of patients achieving a blood eosinophil count of <600 cells/ μ L for ≥ 8 consecutive weeks. Adapted from Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, et al. Treatment of the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008;358:1215-28.⁴⁶

investigator to be related to mepolizumab and did not result in withdrawal. One potential infusion reaction during the first dose of mepolizumab was considered by the investigator to be related to mepolizumab and led to study withdrawal. No clinically relevant trends were observed in hematology or clinical chemistry values, vital signs, or electrocardiograms.

In terms of efficacy, mepolizumab sustained the corticosteroid-sparing effects of mepolizumab observed in the preceding pivotal study while maintaining HES disease control. In addition, a reduction in the dose of systemic prednisone to ≤ 10 mg/d for at least 12 weeks was achieved with mepolizumab in 80% of subjects who had received placebo in the index study and were previously unable to attain this response. These corticosteroid-sparing effects were sustainable for the majority of patients when the interval between infusions was increased during the study.

MEPOLIZUMAB IN ASTHMA

Eosinophil infiltration and degranulation in pulmonary airway tissue has been implicated in the pathophysiology of

TABLE II. Summary of mepolizumab clinical experience in patients with asthma

Reference	Design	Subjects	Treatment	Results
Büttner et al ⁵⁴	Multicenter, double-blind, placebo-controlled	Patients with mild or moderate asthma (FEV ₁ 50% to 80% predicted, with ≥12% reversibility; on ≤1000 µg beclomethasone or equivalent for ≥6 wk) 20-59 years of age n = 19	Mepolizumab 250 mg (n = 7) or 750 mg (n = 5) or placebo (n = 7) IV at intervals of 4 wk for 3 mo 3-mo follow-up	Blood eosinophil count: ● Rapid and sustained reduction (median values from 300 to 45/µL; <i>P</i> < .05 vs placebo) Serum eosinophil cationic protein levels: ● Rapid and sustained reduction paralleling reduction in eosinophil count (median values from 15 to 5 µg/L; <i>P</i> < .05 vs placebo) No change in peripheral blood T-cell subset counts or T-cell cytokine production No asthma-related functional endpoints were evaluated
Leckie et al ⁵³ Study SB-240563/001	Multicenter, double-blind, randomized, placebo-controlled	Men with mild atopic asthma (FEV ₁ ≥70% predicted; on β ₂ -agonists) 18-45 years of age n = 24	One IV dose of mepolizumab 2.5 mg/kg (n = 8) or 10 mg/kg (n = 8), or placebo (n = 8) on day 1 Inhaled histamine and allergen challenges on days 8 and 29, with sputum induction on days 9 and 30 16-wk follow-up	Blood eosinophil count: ● Day 8: 0.26 × 10 ⁹ /L with placebo; 0.24 × 10 ⁹ /L with mepolizumab 2.5 mg/kg; 0.08 × 10 ⁹ /L with mepolizumab 10 mg/kg (<i>P</i> = .0054 vs placebo) ● Day 29: 0.25 × 10 ⁹ /L with placebo; 0.23 × 10 ⁹ /L with mepolizumab 2.5 mg/kg; 0.04 × 10 ⁹ /L with mepolizumab 10 mg/kg (<i>P</i> < .0001 vs placebo) ● Suppression maintained to week 16 Postallergen challenge blood eosinophil count: ● Day 9: 0.44 × 10 ⁹ /L with placebo; 0.12 × 10 ⁹ /L with mepolizumab 2.5 mg/kg (<i>P</i> = .0012 vs placebo); 0.10 × 10 ⁹ /L with mepolizumab 10 mg/kg (<i>P</i> = .0006 vs placebo) ● Day 29: 0.52 × 10 ⁹ /L with placebo; 0.09 × 10 ⁹ /L with mepolizumab 2.5 mg/kg (<i>P</i> = .0002 vs placebo); 0.04 × 10 ⁹ /L with mepolizumab 10 mg/kg (<i>P</i> < .0001 vs placebo) Postallergen challenge sputum eosinophils (mean % of total leukocytes): ● Day 9: 12.2% with placebo; 7.2% with mepolizumab 2.5 mg/kg; 0.9% with mepolizumab 10 mg/kg (<i>P</i> = .0076 vs placebo) ● Day 30: 12.8% with placebo; 6.8% with mepolizumab 2.5 mg/kg; 0.7% with mepolizumab 10 mg/kg (<i>P</i> = .005 vs placebo) No significant effect on the late asthmatic response to allergen challenge (evaluated as the % decrease in FEV ₁), or on airway hyperresponsiveness to inhaled histamine
Flood-Page et al ⁵⁶ Study SB-240563/006	Multicenter, double-blind, randomized, placebo-controlled	Patients with moderate persistent asthma (FEV ₁ 50% to 80% predicted, with ≥12% reversibility; on 400 to 1000 µg beclomethasone or equivalent for ≥6 wk) 18-55 years of age n = 362	Three IV doses of mepolizumab 250 mg (n = 120) or 750 mg (n = 116), or placebo (n = 126) at intervals of 1 mo 8-wk follow-up	Blood eosinophil count: ● Rapid and marked reduction from baseline of approximately 80% with mepolizumab 250 mg and 750 mg (<i>P</i> < .001 vs placebo) ● Sustained until final follow-up visit Sputum eosinophil count: ● Significant reductions vs baseline (<i>P</i> = .006 for mepolizumab 250 mg, <i>P</i> = .004 for mepolizumab 750 mg) and vs placebo (<i>P</i> = .005 for mepolizumab 250 mg, <i>P</i> = .001 for mepolizumab 750 mg) ● Sustained until final follow-up visit Few statistically significant differences between mepolizumab 250 mg or 750 mg and placebo in the change from baseline to study end in morning domiciliary PEFR, FEV ₁ , daily β ₂ -agonist use, symptom scores, quality of life measures, or asthma exacerbation rates ● Significantly greater increase in PEFR with mepolizumab 250 mg vs placebo at final follow-up visit (<i>P</i> = .039) ● Significantly greater decrease in summary symptom score (indicating improvement) with placebo vs mepolizumab 750 mg at week 12 (4 wk after the final dose; <i>P</i> = .032)

Flood-Page et al ⁴⁷ Menzies-Gow et al ⁵⁵ Flood-Page et al ⁵⁹ Phipps et al ⁶² Study SB-240563/036	Double-blind, randomized, placebo-controlled, parallel-group	Patients with mild atopic asthma (FEV ₁ ≥70% predicted, on β ₂ -agonists) Nonsmokers 18-55 years of age n = 24	Three IV doses of mepolizumab 750 mg (n = 11) or placebo (n = 13) at intervals of 4 wk 12-wk follow-up	● Nonsignificant trend for a reduction in rates of level 2 and 3 exacerbation rates over weeks 12-20 with mepolizumab 750 mg vs placebo ($P = .065$)
				Blood eosinophil count: ● Significant reduction at week 4 ($P = .002$ vs placebo) and week 10 ($P = .02$ vs placebo) ● Median reduction of 100% from baseline (interquartile range, 67% to 100%) Bronchial mucosa eosinophils: ● Median reduction of 55% from baseline (interquartile range, 29% to 89%; $P = .009$ vs placebo) Bone marrow eosinophils: ● Median reduction of 52% from baseline (interquartile range, 45% to 76%; $P = .003$ vs placebo) ● 70% reduction in number of mature eosinophils vs placebo ($P = .017$) ● 37% reduction in number of myelocytes vs placebo ($P = .006$) ● 44% reduction in number of metamyelocytes vs placebo ($P = .003$) Bronchoalveolar fluid eosinophils: ● Median reduction of 79% from baseline (interquartile range, 43% to 99%; $P = .4$ vs placebo) Cutaneous eosinophil infiltration: ● Significant reduction with mepolizumab vs placebo 6 hours after allergen challenge (−83% vs +33%; $P = .0015$) ● Significant reduction with mepolizumab vs placebo 48 h after allergen challenge ($P = .0025$) No significant difference between mepolizumab and placebo for airway hyperresponsiveness, FEV₁, or PEFr No significant differences vs placebo in blood or bone marrow CD34⁺ or CD34⁺/IL-5Rα⁺ cells, bone marrow-derived eosinophil/basophil colony-forming units, or bronchial mucosa CD34⁺/IL-5Rα mRNA⁺ cells Extracellular matrix protein expression in bronchial mucosal reticular basement membrane: ● Significant reduction in tenascin thickness ($P = .008$), density ($P = .003$), and total expression ($P = .004$) vs placebo ● Significant reduction in lumican density ($P = .05$) and total expression ($P = .008$) vs placebo ● Significant reduction in procollagen III density ($P = .05$) and total expression ($P = .007$) vs placebo TGF-β1 expression: ● Significant reduction in number ($P = .03$) and percentage ($P = .04$) of bronchial mucosa eosinophils expressing TGF-β1 mRNA vs placebo ● Significant reduction in concentration of TGF-β1 in bronchoalveolar fluid with mepolizumab vs placebo ($P = .042$) Major basic protein-degranulating eosinophils in skin biopsies: ● Significant reduction with mepolizumab vs placebo 6 hours after allergen challenge ($P = .029$); nonsignificant at 48 hours Tenascin-positive cells in skin biopsies: ● Significant reduction with mepolizumab vs placebo 48 hours after allergen challenge ($P = .0256$); nonsignificant at 6 hours No significant effect on the 6-h or 48-h late-phase cutaneous reaction to allergen challenge

(Continued)

TABLE II. (Continued)

Reference	Design	Subjects	Treatment	Results
Nair et al ⁵⁷ Study SB-240563/046	Double-blind, randomized, placebo-controlled, pilot study	Patients with prednisone- dependent asthma with persistent sputum eosinophilia >3% 18-70 years of age n = 20	Five IV doses of mepolizumab 750 mg (n = 9) or placebo (n = 11) at intervals of 1 mo Prednisone dose tapered after the second infusion according to a prespecified schedule 8-wk follow-up	Asthma exacerbations: ● Significant reduction in number of patients with exacerbations during prednisone tapering with mepolizumab (1 exacerbation) vs placebo (12 exacerbations in 10 patients; $P < .01$) ● Median time to exacerbation was 20 wk with mepolizumab vs 12 wk with placebo ($P = .003$) Prednisone-sparing: ● Significant reduction in prednisone dose, as a percentage of the maximum dose reduction possible without a clinical exacerbation, with mepolizumab (mean $\pm$ SD, 83.8% $\pm$ 33.4%) vs placebo (47.7% $\pm$ 40.5%; $P = .04$) Blood eosinophil count (mean $\pm$ SD): ● Mepolizumab: significant reduction from baseline (664.4 $\pm$ 492.5/μL) at 4 wk after the first dose (49.5 $\pm$ 37.5/μL), 4 wk after the last dose (64.5 $\pm$ 37.9/μL), and follow-up (76.3 $\pm$ 39.4/μL; $P < .05$) ● Placebo: no significant reduction from baseline (352.1 $\pm$ 253.7/μL) at 4 wk after the first dose (295.8 $\pm$ 207.4/μL), 4 wk after the last dose (657.0 $\pm$ 413.2/μL), or follow-up (1224.0 $\pm$ 1383.0/μL) Sputum eosinophil counts (median): ● Mepolizumab: significant reduction from baseline (16.6%) at 4 wk after the first dose (0%), 4 wk after the last dose (1.3%), and follow-up (0.3%; $P < .05$) ● Placebo: no significant reduction from baseline (4.0%) at 4 wk after the first dose (3.0%), 4 wk after the last dose (3.2%), or follow-up (5.0%) Additional outcomes: ● FEV₁: significantly greater improvement from baseline with mepolizumab vs placebo ($P < .05$) ● Asthma symptoms: nonsignificant improvement from baseline with mepolizumab ● Juniper Asthma Control Questionnaire score: significant improvement from baseline with mepolizumab ($P = .01$)
Haldar et al ⁵⁸	Double-blind, randomized, placebo-controlled, parallel-group	Patients with refractory eosinophilic asthma and a history of recurrent severe exacerbations 21-72 years of age n = 61	Twelve IV doses of mepolizumab 750 mg (n = 29) or placebo (n = 32) at intervals of 1 mo	Severe exacerbations: ● Mean 12-mo exacerbation rates: 2.0 exacerbations per subject with mepolizumab vs 3.4 with placebo (Risk Ratio, 0.57; 95% CI, 0.32-0.92; $P = .02$) Asthma Quality of Life Questionnaire score: ● Mean increase from baseline: 0.55 with mepolizumab vs 0.19 with placebo (mean between-group difference, 0.35; 95% CI, 0.08-0.62; $P = .02$) Additional outcomes: ● Blood eosinophils: significantly greater reduction from baseline vs placebo ($P < .001$) ● Sputum eosinophils: significantly greater reduction from baseline vs placebo ($P = .002$) ● No significant differences between groups in symptoms, FEV₁ after bronchodilator use, or airway hyperresponsiveness

IV, Intravenous; PEFR, peak expiratory flow rate.

asthma,^{1,47,48} and a correlation has been noted between airway eosinophil counts and some features of asthma severity.⁴⁹ Clinical studies have shown that IL-5 is increased in bronchial biopsies from patients with asthma,⁵⁰ concentrations of IL-5 correlate with clinical features of asthma,⁵¹ and IL-5 mRNA is upregulated in bronchial mucosa after allergen challenge.⁵² Thus, IL-5 inhibition may have a beneficial therapeutic effect in asthma by preventing eosinophil maturation, function, or migration into pulmonary tissue.

Placebo-controlled clinical trials have evaluated the efficacy and safety of mepolizumab in more than 300 patients with asthma (Table II).^{47,53-58} Persistent, significant, and dose-dependent reductions in blood eosinophil counts were consistently observed with mepolizumab in these trials; levels of sputum, bronchial mucosa, and bone marrow eosinophils also decreased. Interestingly, in 1 study,⁵⁹ mepolizumab reduced airway eosinophil counts and the expression of extracellular matrix proteins in the bronchial subepithelial basement membrane, suggesting that eosinophils may play a role in tissue remodeling events in patients with asthma.

In the earlier trials involving broad populations of patients with asthma, mepolizumab had no clinically significant effects on functional airways outcome measures. However, a nonsignificant trend for a reduction in more severe exacerbations after the administration of 3 monthly intravenous doses of mepolizumab 750 mg versus placebo was observed in 1 study involving patients with moderate persistent asthma ($P = .065$).⁵⁶ On the basis of these findings and observations that eosinophilic airway inflammation is closely associated with exacerbation frequency,^{60,61} more recent trials evaluated the effects of mepolizumab on exacerbations in subgroups of patients with persistent airway eosinophilia despite corticosteroid treatment.^{57,58} In these trials, mepolizumab significantly reduced exacerbation rates in patients with refractory eosinophilic asthma (defined as sputum eosinophilia >3% despite systemic corticosteroid treatment) and a history of severe exacerbations⁵⁸ and in those with steroid-dependent asthma with sputum eosinophilia (Table II).⁵⁷ The authors speculated that previous studies with mepolizumab in asthma failed to show functional benefits for several reasons: (1) the study populations were not selected on the presence of persistent airway eosinophilia despite appropriate doses of corticosteroids, (2) study durations were insufficiently long to evaluate the effect of mepolizumab on exacerbations adequately, and (3) the clinical outcomes that were assessed might be dissociated from eosinophilic inflammation and are improved by corticosteroids via alternative mechanisms. These preliminary studies indicate the importance of a careful, phenotypic selection of patients in whom eosinophils remain present despite either topical or systemic corticosteroid use. Under these conditions, eosinophils appear to contribute to mechanisms of asthma, especially exacerbations. Additional clinical trials are planned to define further the population of patients with refractory asthma likely to derive clinical benefit from treatment with mepolizumab.

Mepolizumab was well tolerated in all the asthma trials. No serious risks associated with mepolizumab or clear predisposing factors for adverse events were identified.

MEPOLIZUMAB IN OTHER DISEASE STATES

Mepolizumab has also been evaluated in other disease states in which eosinophils are implicated in the pathology. These include

atopic dermatitis,⁶²⁻⁶⁵ eosinophilic esophagitis,^{66,67} nasal polyposis,⁶⁸ and Churg-Strauss syndrome.⁶⁹ Clinical improvements were variable among the conditions, with clear clinical benefits observed in patients with severe nasal polyposis.⁶⁸ However, a lack of efficacy in atopic diseases was noted, which is consistent with immunologic data observed in patients with asthma receiving mepolizumab, in whom no changes in peripheral blood T-cell subset counts or T-cell cytokine production were seen during antibody treatment.⁵⁴ In all cases, mepolizumab was generally well tolerated and raised no major safety concerns. There were few serious adverse events (none considered drug-related), and few withdrawals as a result of adverse events. Additional ongoing exploratory studies are assessing the use of mepolizumab in patients with eosinophilic cystitis and Churg-Strauss syndrome.

Eosinophils are implicated in several disease states, including HESs and phenotypes of severe asthma. IL-5 is vital for eosinophil development and function. Thus, inhibition of IL-5 activity can be expected to deplete the numbers of circulating eosinophils and their activation in target tissues and have benefit in diseases in which eosinophils contribute to the pathophysiology.

Multiple processes are involved in the regulation of eosinophilopoiesis in the bone marrow, recruitment of eosinophils to tissues and their survival, and the activation and secretion of inflammatory mediators. The recognition that heterogeneity likely exists in eosinophil biology and the resulting clinical phenotypes has hampered the development of specific, effective treatments for HESs and other diseases in which eosinophils persist. In HESs, chronic systemic corticosteroids are the first-line treatment for *FIPILI-PDGFR*-negative patients with symptomatic disease. Because of their nonspecific activity, however, use of chronic corticosteroids is associated with poor tolerability.^{70,71} Reducing the level of corticosteroid dependency may be expected to decrease the toxicity and morbidity associated with these drugs. It should be noted here that the Marketing Authorisation Application for mepolizumab in the treatment of *FIPILI-PDGFR*-negative HES was withdrawn from the European Medicines Agency in 2009. The European Medicines Agency considered that there was insufficient evidence to demonstrate long-term clinical efficacy other than a significant reduction in corticosteroid use.

Early trials in selected patients with severe asthma support a role for anti-IL-5 treatment. Additional clinical trials will further assess the potential for mepolizumab in the treatment of refractory asthma.

Collectively, these clinical trial observations not only provide potentially new treatment approaches but also have given insight into the regulation of disease mechanisms in HESs and asthma. On the basis of this information, safe and effective treatment options are emerging that might be more directed toward the mechanisms of an individual patient's disease and result in more predictable and effective outcomes.

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