Nucala (Mepolizumab): First IL-5 Antagonist Monoclonal Antibody FDA Approved for Maintenance Treatment of Patients with Severe Asthma

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Asthma, a condition characterized by the narrowing and inflammation of airways and excess mucus, affects 1 in 12 individuals in the United States—approximately 25 million people, or 8% of the US population.[1] Overall, 53% of patients with asthma experience an asthma attack (ie, exacerbation) annually.[1]

Although asthma therapy, when used according to the current management guidelines, controls the disease in the majority of patients, an estimated 10% of patients have severe asthma, characterized by reduced responsiveness to standard therapy, as well as increased morbidity and reduced quality of life.[2,3] Severe asthma exacerbations often lead to hospitalization and can be life-threatening.[4] Overall, asthma exacerbations can result in substantial morbidity, mortality, and healthcare utilization and associated costs.[5] According to the Centers for Disease Control and Prevention, asthma accounts for an estimated 3630 deaths annually in the United States, and 1.8 million emergency department visits with asthma as the primary diagnosis.[6] In addition, there are 439,000 asthma-related hospitalizations annually, with an average length of stay of 3.6 days.[6]

In the United States, asthma costs accounted for $56 billion annually in 2007, representing a 6% increase from $53 billion in 2002.[1] Between 2002 and 2007, the annual per-person cost for patients with asthma was $3300 in medical expenses, missed school or work days, and early mortality.[1]

The diagnostic tests for asthma may include spirometry or a peak flow meter to measure lung function.[7] Other diagnostic tools may include imaging; allergy tests; a nitric oxide test; methacholine response; provocative tests (postphysical activity); or a sputum eosinophils test, which measures the presence of eosinophils in the saliva and sputum.[7]

Eosinophils play a role in asthma-related airway inflammation.[8] Some patients with eosinophilic airway inflammation experience recurrent asthma exacerbations, despite receiving inhaled glucocorticoid treatment (with or without oral glucocorticoids); long-term use of oral glucocorticoids is associated with potentially serious adverse reactions.[2,9,10]

The management of asthma includes the recognition and avoidance of disease triggers, ongoing control of symptoms, and, in the event of a flare-up, the use of a quick-relief (rescue) inhaler, such as albuterol.[11] Long-term control medications include inhaled corticosteroids, leukotriene modifiers, long-acting beta agonists, combination inhalers, and theophylline.[11] Rescue medications include the short-acting beta agonists, the anticholinergic bronchodilator ipratropium, and oral and intravenous (IV) corticosteroids.

For asthma that is worsened by allergies, pharmacotherapy options include immunotherapy (ie, allergy shots) or omalizumab.[11] There is a need for additional treatment options for patients with severe asthma and the eosinophilic phenotype.[4,11]

Mepolizumab Approved for Maintenance Treatment in Severe Asthma

On November 4, 2015, mepolizumab (Nucala; GlaxoSmithKline), a humanized, interleukin-5 (IL-5) antagonist monoclonal antibody, was approved by the US Food and Drug Administration (FDA) as an add-on subcutaneous maintenance treatment for patients aged ≥12 years with an eosinophilic phenotype who have severe asthma.[4,8] Mepolizumab is not indicated for the treatment of other eosinophilic conditions, or for the relief of acute bronchospasm or status asthmaticus.[8] Mepolizumab is the first FDA-approved biologic agent that targets IL-5, which regulates the function of eosinophils.[12]

Badrul Chowdhury, MD, PhD, Director of the FDA's Division of Pulmonary, Allergy, and Rheumatology Products, commented, "This approval offers patients with severe asthma an additional therapy when current treatments cannot maintain adequate control of their asthma."[4]

According to Professor Ian Pavord, University of Oxford, an investigator for a phase 3 clinical trial with mepolizumab, "Severe asthma is a debilitating condition in which patients are at high risk of frequent and serious

asthma attacks. Half of all severe asthma patients have at least one urgent care visit per year. As a clinician, the prospect of a treatment that can specifically target the underlying cause of the disease for patients whose condition is driven by eosinophilic inflammation is exciting."[11]

Mechanism of Action

Mepolizumab is a humanized, IL-5 antagonist monoclonal antibody (immunoglobulin G1 kappa).[8] The IL-5 cytokine regulates the growth, recruitment, activation, and life cycle of eosinophils—one of several cell types involved in asthma-related airway inflammation.[8]

Mepolizumab controls severe asthma exacerbations by reducing the levels of blood eosinophils that contribute to the pathogenesis of asthma.[4] Mepolizumab binds to IL-5 and inhibits IL-5 signaling, thereby reducing the production and survival of eosinophils; however, the exact mechanism of action of mepolizumab in asthma has not been firmly established.[8]

Dosing and Administration

Mepolizumab injection is available as 100 mg of lyophilized powder in a single-dose glass vial for reconstitution. Mepolizumab 100 mg is administered via subcutaneous injection once every 4 weeks by a healthcare professional into the upper arm, thigh, or abdomen.[8]

Before administration, mepolizumab is reconstituted in a vial with sterile water, as instructed in the prescribing information. Patients should be monitored after the administration of mepolizumab, as is the standard clinical practice after the administration of a biologic agent.[8]

Clinical Trials

The clinical development program that evaluated mepolizumab in patients with asthma included 3 double-blind, randomized, placebo-controlled studies, including Study 1 (DREAM), a dose-ranging and exacerbation clinical trial, and Study 2 (MENSA) and Study 3 (SIRIUS)—2 confirmatory trials.[2,5,8,9]

In all 3 studies, mepolizumab was administered every 4 weeks as an add-on treatment to background treatment, with patients continuing their background asthma therapy throughout the duration of the study.[8] To be included in the 2 confirmatory clinical trials, patients had to have blood eosinophils levels ≥150 cells/mcL at screening (within 6 weeks of dosing) or blood eosinophils levels ≥300 cells/mcL within 12 months of enrollment (**Table 1**).

Table 1 Mepolizumab Studies 1, 2, and 3: Patient Baseline Characteristics

Patient characteristics	Study 1 (N = 616)	Study 2 (N = 576)	Study 3 (N = 135)
Mean age, yrs	49	50	50
Female, N (%)	387 (63)	328 (57)	74 (55)
White, N (%)	554 (90)	450 (78)	128 (95)
Duration of asthma, mean, yrs	19	20	19
Never smoked, N (%)	483 (78)	417 (72)	82 (61)
Baseline FEV_1, L	1.88	1.82	1.95
Baseline predicted FEV_1, %	60	61	59
Baseline reversibility, %	25	27	26
Baseline post-SABA FEV_1/FVC	0.67	0.66	0.66
Geometric mean eosinophil count at baseline, cells/mcL	250	290	240
Mean exacerbations in previous year, N	3.6	3.6	3.1

FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; SABA, short-acting beta$_2$-agonist.
Source: Nucala (mepolizumab) for injection prescribing information; November 2015.

Study 1 (DREAM): Dose-Ranging and Exacerbation Trial

The findings from Study 1 (DREAM)—a 52-week, dose-ranging and exacerbation-reduction clinical trial—and the findings from a pharmacodynamic study supported the evaluation of mepolizumab 100 mg administered subcutaneously and mepolizumab 75 mg administered intravenously in subsequent clinical trials; however, mepolizumab was ultimately approved by the FDA for subcutaneous administration only.[5,8]

Study 2 (MENSA): Confirmatory Trial

The MENSA study, a 32-week clinical trial, included patients with asthma who had a history of ≥2 exacerbations in the previous year, despite regular treatment with high-dose inhaled corticosteroids plus an additional controller, with or without oral corticosteroids.[8,9]

Results from Study 1 and 2

The primary end point for Study 1 and 2 was the frequency of exacerbation, defined as the worsening of asthma necessitating the use of an oral or systemic corticosteroid and/or hospitalization and/or emergency department visits.[8]

Study 2 results showed that the time to the first exacerbation was longer in patients who received subcutaneous mepolizumab 100 mg and IV mepolizumab 75 mg compared with placebo.[8,9] In both studies, patients who received subcutaneous mepolizumab 100 mg and IV me-

polizumab 75 mg had significantly fewer exacerbations compared with patients who received placebo (**Table 2**). Furthermore, patients in the mepolizumab group had fewer exacerbations that required hospitalization and/or emergency department visits and exacerbations requiring only in-patient hospitalization compared with the placebo group.[8]

Study 3 (SIRIUS): Confirmatory Trial

SIRIUS, a 24-week clinical trial, evaluated the effect of mepolizumab on reducing the use of maintenance oral corticosteroids; the primary efficacy outcome was the percent reduction of the oral corticosteroid dose in weeks 20 to 24 compared with the baseline dose, while maintaining asthma control.[8]

Treatment with mepolizumab demonstrated a significant glucocorticoid-sparing effect compared with placebo (**Table 3**).[8] Mepolizumab was 2.39 times more likely to reduce glucocorticoid doses versus placebo (95% confidence interval, 1.25-4.56; P = .008).[2]

Lung Function: Study 1, 2, and 3

In Study 1, 2, and 3, treatment with mepolizumab did not show consistent improvements in the mean change from baseline in the forced expiratory volume in 1 second (**Table 4**).[8]

Adverse Reactions

The most common adverse reactions (≥5% incidence) associated with mepolizumab were headache (19%), injection-site reaction (8%), back pain (5%), and fatigue (5%).[8]

Based on the data from the 3 randomized, placebo-controlled studies lasting 24 to 52 weeks, 2% of patients receiving mepolizumab withdrew from the studies because of adverse events compared with 3% of patients receiving placebo.[8] One serious adverse event (herpes zoster) occurred in 2 patients who received mepolizumab versus none in patients receiving placebo. Additional cases of herpes zoster have been reported in ongoing open-label, extension clinical trials in the 998 patients receiving mepolizumab.[8]

Overall, 6% (15/260) of patients who received mepolizumab developed antimepolizumab antibodies, which increased by approximately 20% the clearance of mepolizumab.[8] The clinical relevance of these antimepolizu-

Table 2 Mepolizumab versus Placebo: Rate of Exacerbations in Study 1 and 2 (Intent-to-Treat Population)

Study	Treatment	Exacerbations, annually		
		Rate	Difference	Rate ratio
All exacerbations				
Study 1	Placebo[a]	2.40		
	Mepolizumab 75 mg IV[b]	1.24	1.16	0.52 (95% CI, 0.39-0.69)
Study 2	Placebo[c]	1.74		
	Mepolizumab 75 mg IV[c]	0.93	0.81	0.53 (95% CI, 0.40-0.72)
	Mepolizumab 100 mg SC[d]	0.83	0.91	0.47 (95% CI, 0.35-0.64)
Exacerbations requiring hospitalization and/or emergency department visit				
Study 1	Placebo[a]	0.43		
	Mepolizumab 75 mg IV[b]	0.17	0.26	0.40 (95% CI, 0.19-0.81)
Study 2	Placebo[c]	0.20		
	Mepolizumab 75 mg IV[c]	0.14	0.06	0.68 (95% CI, 0.33-1.41)
	Mepolizumab 100 mg SC[d]	0.08	0.12	0.39 (95% CI, 0.18-0.83)
Exacerbations requiring hospitalization				
Study 1	Placebo[a]	0.18		
	Mepolizumab 75 mg IV[b]	0.11	0.07	0.61 (95% CI, 0.28-1.33)
Study 2	Placebo[c]	0.10		
	Mepolizumab 75 mg IV[c]	0.06	0.04	0.61 (95% CI, 0.23-1.66)
	Mepolizumab 100 mg SC[d]	0.03	0.07	0.31 (95% CI, 0.11-0.91)

[a]N = 155; [b]N = 153; [c]N = 191; [d]N = 194.
CI indicates confidence interval; IV, intravenous; SC, subcutaneous.
Source: Nucala (mepolizumab) for injection prescribing information; November 2015.

Table 3 Mepolizumab versus Placebo: Oral Glucocorticoid-Sparing Effect in Study 3

Outcome	Mepolizumab, N (%)	Placebo, N (%)
Patients achieving a 90%-100% reduction in oral corticosteroid dose	16 (23)	7 (11)
Patients who achieved at least a 50% reduction in the daily prednisone dose	37 (54)	22 (33)
Patients with no reduction in oral glucocorticoid dose, a lack of asthma control, or treatment withdrawal	25 (36)	37 (56)

Sources: Nucala (mepolizumab) for injection prescribing information; November 2015; Bel EH, et al. *N Engl J Med*. 2014;371:1189-1197.

Table 4 Mepolizumab versus Placebo: Change from FEV_1 Baseline in Study 1, 2, and 3

	Difference from placebo in mean change from baseline FEV_1		
Clinical study	Week 12, mL	Week 24, mL	Weeks 32/52, mL
Study 1 (75-mg IV)	10 (95% CI, –87 to 108)	5 (95% CI, –98 to 108)	61 (95% CI, –39 to 161)[a]
Study 2 (100-mg SC)	52 (95% CI, –30 to 134)	76 (95% CI, –6 to 159)	98 (95% CI, 11 to 184)[b]
Study 3 (100-mg SC)	56 (95% CI, –91 to 203)	114 (95% CI, –42 to 271)	N/A

[a]FEV_1 at week 52.
[b]FEV_1 at week 32.
CI indicates confidence interval; FEV_1, forced expiratory volume in 1 second; IV, intravenous; N/A, not applicable; SC, subcutaneous.
Source: Nucala (mepolizumab) for injection prescribing information; November 2015.

mab antibodies is unknown; there was no evidence that these antibody titers effected changes in the blood eosinophil levels.[8]

Contraindications

Mepolizumab is contraindicated in patients with a history of hypersensitivity to mepolizumab or its excipients in the formulation.[8]

Warnings and Precautions

Hypersensitivity reactions. Hypersensitivity reactions (eg, angioedema, bronchospasm, hypotension, rash, urticaria) have been reported after mepolizumab administration; mepolizumab should be discontinued in a patient with hypersensitivity reaction.[8]

Acute asthma symptoms or deteriorating disease. Mepolizumab should not be used for the treatment of patients with acute asthma symptoms, acute exacerbations, acute bronchospasm, or status asthmaticus. Patients whose asthma worsens or remains uncontrolled after initial treatment with mepolizumab should seek medical advice.[8]

Herpes zoster. In clinical studies, 2 serious herpes zoster adverse reactions occurred in patients who received mepolizumab. Varicella vaccination should be considered before starting treatment with mepolizumab.[8]

Reduction of corticosteroid dosage. Systemic or inhaled corticosteroids should not be discontinued abruptly when initiating treatment with mepolizumab. Any reductions of the corticosteroid dose should be gradual and performed under a physician's direct supervision.[8]

Helminth infection. Patients with preexisting helminth infections should receive treatment before starting mepolizumab therapy. If a patient is helminth-infected while receiving mepolizumab and does not respond to antihelminth treatment, mepolizumab should be discontinued until the infection resolves.[8]

Use in Specific Populations

Pregnancy. Clinical trial data on mepolizumab exposure during pregnancy are insufficient to determine drug-associated risks. It is recommended that healthcare providers enroll patients in a pregnancy exposure registry to monitor pregnancy outcomes in women exposed to mepolizumab during pregnancy.[8]

Lactation. No data are available on the presence of mepolizumab in human milk, its effects on breastfed infants, or its effects on the production of milk.[8]

Pediatric use. The safety and efficacy of mepolizumab in patients aged ≤12 years have not been determined.[8]

Geriatric use. There were insufficient numbers of patients aged ≥65 years in the mepolizumab clinical trials to determine whether their treatment response was different from that of younger patients. The dose selection for elderly patients should start at the low end of the dosing range. Available data suggest that no dosage adjustment is required in geriatric patients, but the potential for increased sensitivity should be considered.[8]

Conclusion

The FDA approval of mepolizumab marks the availability of the first biologic agent to target IL-5, a cytokine that regulates the growth, activity, and survival of eosinophils—the inflammatory cells that play a key role in the pathogenesis of asthma. Mepolizumab, an IL-5 antagonist monoclonal antibody administered subcutaneously once monthly, is indicated as an add-on maintenance treatment for patients aged ≥12 years with severe asthma, and with an eosinophilic phenotype.

In clinical trials, patients who received mepolizumab had significantly fewer exacerbations than patients receiving placebo. Patients who received mepolizumab also had fewer exacerbations requiring hospitalization and/or emergency department visits, and fewer exacerbations requiring in-patient hospitalization compared with placebo. Treatment with mepolizumab was more than twice as likely to reduce glucocorticoid doses as placebo. ■

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