

Mepolizumab (Nucala) For Severe Eosinophilic Asthma

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INTRODUCTION

Asthma, a prevalent chronic inflammatory disease of the airways, affects an estimated 22 million adult Americans.¹ Severe asthma affects approximately 5% to 10% of patients with asthma; exacerbations requiring hospitalization and ongoing treatment account for a majority of morbidity and mortality related to the disease and comprise a significant portion of health care costs.²

Severe asthma is defined as disease that can only be controlled with high-dose inhaled corticosteroids plus a second maintenance medication and/or systemic corticosteroids, or that remains uncontrolled despite optimal therapy.² Severe asthma is increasingly recognized as a heterogeneous condition, as evidenced by different underlying mechanisms, clinical presentations, physiologic characteristics, and outcomes.²

Recurrent asthma exacerbations are of particular concern in the subsets of patients consisting of specific phenotypes, such as eosinophilic asthma. The eosinophilic phenotype is not well defined, but patients in this group generally have severe disease with high blood and

sputum eosinophil levels despite treatment with high-dose inhaled corticosteroids and systemic corticosteroids.² Interleukin (IL)-5 is the major cytokine that plays a vital role in eosinophil production, proliferation, and chemotaxis.³ Furthermore, recent findings strongly suggest that the presence of airway eosinophilia is clinically relevant and suggest that blocking IL-5 at its receptor represents a promising treatment strategy for certain individuals.³

Studies of novel biologic therapies targeting and mitigating specific asthmatic inflammatory pathways have reported positive results and are beginning to help define immuno-inflammatory phenotypes. This review will focus on the safety and efficacy of mepolizumab (Nucala, GlaxoSmithKline), an IL-5 antagonist monoclonal antibody approved by the Food and Drug Administration in November 2015 as an add-on maintenance treatment for severe asthma in patients 12 years of age or older whose exacerbations are eosinophilic related.

PHARMACOLOGY AND PHARMACODYNAMICS

Mepolizumab is a fully humanized monoclonal antibody that targets IL-5 with high affinity and specificity, and prevents binding to the IL-5 receptor on the surface of eosinophils.⁴ IL-5 is one of the most important cytokines in the development and activation of eosinophils, which

are associated with inflammation and diseases such as asthma, atopic dermatitis, and hypereosinophilic syndrome.^{4,5} Though IL-5 is also expressed in basophils, IL-3 is more potent than IL-5 in the survival and development of basophils.⁵

In asthmatic patients with blood eosinophil levels greater than 200 cells/mcL, blood eosinophils were reduced in a dose-dependent manner to a geometric mean count of 40 cells/mcL following subcutaneous (SC) administration of 100 mg of mepolizumab, representing an average reduction of 84% compared with placebo.⁵

PHARMACOKINETICS

A summary of the pharmacokinetic characteristics of mepolizumab can be found in Table 1.

Healthy Subjects

In an open-label, single-dose, randomized, parallel-group, 12-week trial (N = 60; 12 patients in each arm), 250 mg of mepolizumab was administered as a 30-minute intravenous (IV) infusion; an SC injection in the abdomen, arm, or thigh; or intramuscularly (IM) in the lateral thigh. SC injection of mepolizumab in the abdomen, arm, or thigh resulted in 64%, 75%, and 71% bioavailability compared with 81% bioavailability when administered via the IM route. IV mepolizumab achieved a maximum plasma concentration (C_{max}) at 0.5–4.8 hours after the start of the

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Table 1 Pharmacokinetic Characteristics of Mepolizumab^{4,5}

Absorption	Bioavailability is approximately 80% after 100-mg subcutaneous administration in the upper arm of patients with asthma.
Distribution	Volume of distribution in a 70-kg patient is approximately 3.6 L.
Metabolism	Mepolizumab is degraded by proteolytic enzymes distributed throughout the body and not confined to the hepatic tissue.
Elimination and excretion	- Mean terminal half-life of mepolizumab ranged from 16–22 days. - The specific route of elimination is unknown. - Pharmacokinetics are similar to those of immunoglobulin G1, which is metabolized by proteases with protection by the neonatal Fc receptor.

infusion compared with two to 14 days for SC and IM administration. Regardless of the route of administration, mepolizumab demonstrated a terminal half-life ($t_{1/2}$) of approximately 20 days in this trial.^{5,6}

Asthmatic Patients

In a multicenter, double-blind, randomized, placebo-controlled, dose escalation study in men with mild atopic asthma ($N = 38$), patients received either mepolizumab, administered as a single weight-based IV infusion at a dose of 0.05 mg/kg, 0.5 mg/kg, 2.5 mg/kg, or 10 mg/kg, or placebo. Plasma concentrations decreased biexponentially after IV administration, with a mean initial $t_{1/2}$ of approximately two days followed by a terminal $t_{1/2}$ of approximately 20 days (14–30 days). C_{max} and area under the curve to infinity (AUC_{∞}) exhibited a dose-proportional relationship, and plasma clearance and steady-state volume of distribution data suggested a linear pharmacokinetic profile.⁷

The pharmacokinetics of mepolizumab were also evaluated in a separate multi-dose, double-blind, randomized, placebo-controlled, parallel-group trial ($N = 16$) in male and female patients with mild asthma. Patients received 250-mg abdominal SC doses of mepolizumab ($n = 8$) at weeks 0, 6, and 8. The terminal $t_{1/2}$ and time to maximum concentrations observed were similar to the single-dose studies. Plasma accumulation after the third dose showed a 65% increase in AUC_{∞} and an 80% increase in C_{max} compared with after the first dose.⁸

CLINICAL EFFICACY

Ortega et al.

Ortega and colleagues conducted a phase 3, randomized, double-blind, double-dummy, placebo-controlled trial to evaluate the safety and efficacy of mepolizumab in patients randomized to 75 mg of IV mepolizumab, 100 mg of SC mepolizumab, or placebo once every four weeks for 32 weeks.⁹ A total of 576 patients with recurrent asthma exacerbations and eosinophilic inflammation despite high doses of inhaled glucocorticoids were included.

The primary outcome was the rate of clinically significant asthma exacerbations, defined as worsening asthma requiring systemic glucocorticoids for at least three days, necessitating

care in the emergency department or hospitalization. A total of 449 significant exacerbations were reported. Exacerbation rates decreased to 0.93 per year with the 75-mg IV dose and to 0.83 per year with the 100-mg SC dose versus 1.74 per year for placebo. The relative reduction in exacerbation rates compared with placebo was 47% (95% confidence interval [CI], 28–60) for IV mepolizumab and 53% (95% CI, 36–65) for SC mepolizumab ($P < 0.001$ for both comparisons).

Secondary outcomes such as lung function, quality of life, asthma control, patient and clinician experience, and blood eosinophil count were better in the actively treated groups compared with placebo.⁶ However, a 12-month observational study found that within three months of stopping mepolizumab, blood and sputum eosinophil counts increased significantly, which correlated with the loss of asthma control.¹⁰

Bel et al.

The glucocorticoid-sparing effect of mepolizumab was evaluated in a phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel-group study of 135 patients.¹¹ Eligible patients had to have used a maintenance systemic glucocorticoid regimen consisting of a prednisone dose equivalent to 5–35 mg daily for at least six months prior to enrollment, and had to have blood eosinophil levels of 300 cells/mcL or greater during the 12 months prior to screening or 150 cells/mcL during the optimization phase of the trial. All patients received maintenance high-dose inhaled glucocorticoid therapy and additional rescue inhaler therapy as needed.

The trial had four phases. During the optimization phase (three to eight weeks prior to the start of the study), the lowest dose of systemic glucocorticoid necessary to control asthma symptoms was established. In the induction phase (weeks 0–4), patients were randomized 1:1 and assigned to receive 100 mg of SC mepolizumab or placebo once every four weeks in conjunction with the optimized glucocorticoid dose. In the reduction phase (weeks 4–20), oral glucocorticoid therapy was decreased further based on a predetermined schedule every four weeks. Finally, during the maintenance phase (weeks 20–24), there

were no additional alterations made to the oral glucocorticoid dose. A final safety follow-up visit was conducted at week 32.

The primary efficacy outcome was the percentage reduction in daily oral glucocorticoid therapy in weeks 20 to 24 compared with the glucocorticoid dose determined during the optimization phase. Comparison was based on five categories: 90% to 100% reduction; 75% to less than 90% reduction; 50% to less than 75% reduction; more than zero to less than 50% reduction; and no reduction at all.

Mepolizumab was associated with a significant reduction in oral glucocorticoid dose at 20 to 24 weeks (odds ratio, 2.39; 95% CI, 1.25–4.56; $P = 0.008$). The mepolizumab group experienced an annual asthma exacerbation rate of 1.44 per year compared with 2.12 per year in the placebo group, corresponding to a relative reduction rate of 32% ($P = 0.04$). There were also significant improvements in Asthma Control Questionnaire 5 and St. George's Respiratory Questionnaire scores and greater improvements in forced expiratory volume in one second (FEV_1) from baseline in the treatment group compared with placebo.¹¹

The most frequently reported adverse events in both the placebo and mepolizumab groups were headache and nasopharyngitis. Seven patients (four receiving mepolizumab and three receiving placebo) experienced systemic reactions, and six patients (four receiving mepolizumab and two receiving placebo) experienced local injection-site reactions. Serious adverse effects included hospitalization for asthma exacerbation, which occurred in seven patients receiving placebo, and pneumonia, which occurred in three patients receiving placebo. Positive test results for antimepolizumab antibodies occurred in 4% of patients.¹¹

Compared with a previous study that evaluated the use of 750 mg of IV mepolizumab, this study illustrated that mepolizumab had similar efficacy when given SC at a lower dose, and produced a glucocorticoid-sparing effect, a reduction in the number of annual asthma exacerbations, and improved quality of life.^{11,12}

Flood-Page et al.

This multicenter, randomized, double-blind, placebo-controlled, parallel group trial evaluated the efficacy and safety of

mepolizumab in patients with moderately severe asthma with persistent symptoms despite optimal inhaled corticosteroid use.¹³ Nonsmoking patients 18–55 years of age with asthma on inhaled corticosteroids and with FEV₁ between 50% and 80% were enrolled into three treatment groups: mepolizumab 750 mg, mepolizumab 250 mg, and placebo. The study medication was administered as an IV infusion once every four weeks. The primary endpoint was the change in domiciliary morning peak expiratory flow (PEF) from baseline to weeks 12 and 20.

All three groups had an increase in mean morning PEF, and the mepolizumab 250-mg treatment group had the greater increase compared with the placebo group. However, the change was only 13.5 L/minute ($P = 0.039$). There were significant differences in secondary outcomes such as FEV₁, quality of life, and exacerbation rates. Both mepolizumab treatment groups experienced a significant reduction in blood eosinophils ($P < 0.001$) and sputum eosinophils (250 mg, $P = 0.006$; 750 mg, $P = 0.004$). Other measured parameters did not improve significantly, although there was a trend toward a reduced rate of asthma attacks in patients randomized to the highest dose of mepolizumab ($P = 0.065$).

This study demonstrated that mepolizumab did not seem to add significant clinical benefit for asthmatic patients with persistent symptoms despite inhaled corticosteroid therapy.

SAFETY, TOLERABILITY, AND ADVERSE EFFECTS

A summary of mepolizumab's adverse effects can be found in Table 2.

All three of these early randomized controlled trials showed minimal or no adverse events caused by mepolizumab, and its use was well tolerated.^{9,11,13} The most commonly reported adverse effects were headaches, injection-site reactions, back pain, and fatigue.^{5,9,11,13}

Immunogenicity has been observed in some patients treated with mepolizumab in clinical trials.^{9,11} Notably, Ortega and colleagues reported that 19 patients tested positive for antimepolizumab antibodies (4%, 5%, and 2% for IV mepolizumab, SC mepolizumab, and placebo, respectively).⁹ In the study by Bel et al., six patients (4%) tested positive for antimepolizumab antibodies; five of the six patients had

Table 2 Adverse Effects in Individuals Receiving Mepolizumab Compared With Placebo⁵

Adverse Reaction	Mepolizumab 100 mg (n = 263), %	Placebo (n = 257), %
Headache	19	18
Injection-site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Upper abdominal pain	3	2
Pruritus	3	2
Eczema	3	Less than 1
Muscle spasms	3	Less than 1

non-neutralizing antibodies at low titers, and one patient experienced neutralizing antibodies after the first dose of mepolizumab and at week 32.¹¹ No serious adverse effects attributed to immunogenicity were reported.¹¹

CONTRAINDICATIONS AND PRECAUTIONS

Use of mepolizumab is contraindicated in patients with a history of hypersensitivity to previous doses of the medication.⁵

Risks associated with mepolizumab include hypersensitivity reactions; therefore, mepolizumab must be administered by a health care professional in a monitored office setting.⁵ As with other monoclonal antibody preparations, mepolizumab may increase the risk of opportunistic and parasitic infections. Patients who are being treated for or have active helminth infections, have not had chickenpox or received the varicella vaccine, or are pregnant should report this information to their health care provider in order to determine potential risks. In addition, pregnant women are encouraged to enroll with the Nucala pregnancy registry (www.mothertobaby.org/asthma).⁵

Mepolizumab should not be used to treat acute asthma symptoms or exacerbations, and if asthma is inadequately controlled with mepolizumab, the patient should seek medical help. Reducing systemic or inhaled corticosteroid therapies after initiating mepolizumab should be done under the guidance and monitoring of a health care professional.⁵

DOSAGE, STORAGE, AND ADMINISTRATION

Mepolizumab is available in 100-mg single-dose glass vials as a sterile, preservative-free, lyophilized powder for reconstitution. It should be stored at room temperature in its original package and protected from light prior to use.⁵ Mepolizumab should be reconstituted in the vial with 1.2 mL of sterile water for injection and gently swirled for 10 seconds at 15-second intervals until the powder is dissolved (approximately five minutes). Shaking the solution should be avoided, as this may result in foaming and precipitation.⁵ Before administration by a health care professional, 1 mL (equivalent to 100 mg mepolizumab) of reconstituted mepolizumab solution should be removed from the vial.⁵ Mepolizumab may be administered as an SC injection into the upper arm, thigh, or abdomen once every four weeks.⁵ Patient monitoring for adverse effects and hypersensitivity reactions after administration is recommended.⁵

DRUG INTERACTIONS

There are no known drug interactions for mepolizumab.⁵

COST

The average wholesale price (AWP) for one 100-mg dose of mepolizumab is \$3,090, which amounts to \$37,080 per year (12 doses).¹⁴ This cost must be considered in relation to potentially preventable hospitalization costs, which,

for an asthma exacerbation, are estimated at \$1,502 for an outpatient emergency department visit and more than \$6,600 per hospital stay.^{15,16}

P&T COMMITTEE CONSIDERATIONS

Mepolizumab is a novel drug with many clinical benefits in a select asthmatic population that suffers from recurrent asthmatic exacerbation due to eosinophilic airway inflammation.⁵ While patients suffering from moderate persistent asthma did not derive much clinical benefit from add-on mepolizumab, asthma patients receiving systemic glucocorticoids with a minimum eosinophil count of 150 cells/mcL and recurrent asthma exacerbations experienced better control of asthma symptoms along with reduced exacerbation rates.^{9,11,12} Furthermore, the glucocorticoid-sparing effect of mepolizumab lowers patient exposure to the serious, often irreversible adverse effects of glucocorticoids.¹¹

Omalizumab (Xolair, Genentech), an anti-IgE antibody, may also be considered for use as an add-on therapy for the management of moderate-to-severe persistent asthma in patients who are inadequately controlled on inhaled corticosteroid therapy and have perennial allergen sensitivity.¹⁷ Both mepolizumab and omalizumab require reconstitution prior to administration, have similar adverse effect profiles, and have been shown to reduce asthma exacerbations, reduce glucocorticoid use, and improve asthma control.^{5,17-19} These agents differ, however, in their respective immune targets and indications for use, and are not considered interchangeable. Recent results from a post-hoc analysis suggest that patients with severe eosinophilic asthma previously treated with omalizumab may have a positive response if subsequently treated with mepolizumab.²⁰

The AWP of a 150-mg vial of omalizumab is \$1,134, which results in an annual cost of \$13,608 to \$27,216, depending on the frequency of administration.¹⁴

Because mepolizumab is only indicated for use as a maintenance and add-on therapy, it is better used in hospitals with infusion or outpatient centers, rather than in an inpatient setting.⁵

CONCLUSION

For patients with severe eosinophilic asthma, mepolizumab is an add-on treatment that can be used in conjunction with systemic glucocorticoid therapy. For P&T committees considering this product for formulary addition, mepolizumab represents a treatment option for a specific subset of patients with severe asthma that could be used as adjunctive treatment to improve symptoms, reduce exacerbations, and reduce the dosages of glucocorticoids necessary to control this condition. Ongoing clinical trials evaluating the use of this therapy for eosinophilic granulomatosis, eosinophilic esophagitis, and hypereosinophilic syndrome are under way. Recruitment for a study designed to evaluate conversion from omalizumab to mepolizumab in severe eosinophilic asthma is in progress.

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