

Reslizumab (Cinqair)

An Interleukin-5 Antagonist for Severe Asthma of the Eosinophilic Phenotype

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INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by inflammatory cells, such as basophils, mast cells, macrophages, T cells, T helper cells, and eosinophils, infiltrating the airway. This leads to airway hyper-responsiveness, airflow limitation, and respiratory symptoms.¹ In 2015, approximately 25 million people in the United States were estimated to have asthma, and this number is expected to continue to grow.^{2,3}

Treatment of asthma is dependent on the classification of asthma severity. In patients 12 years of age and older, asthma severity is classified as intermittent or persistent, based on the assessment of impairment and risk.⁴ Impairment is assessed by asthma symptoms and lung function measured via spirometry. Nighttime awakening, frequency of use of short-acting beta₂ agonists for symptomatic relief, missed workdays, and interference with normal activity are all taken into consideration. Assessment of risk is based on the number of exacerbations requiring treatment with oral systemic corticosteroids. The quantification of these components classifies a patient's asthma as intermittent, mild persistent, moderate persistent, or severe persistent (Table 1). The treatment of asthma follows a stepwise approach in which prescribers add medications to patients' regimens according to asthma severity.

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As asthma severity worsens, management of the disease increases to a higher step.⁴ If asthma is well controlled for at least three months, a step down in therapy may be considered (Table 2).⁴

The medications currently available for the treatment of asthma are divided into two classes: rescue drugs and maintenance medications. Rescue medications include short-acting beta agonists and oral corticosteroids.⁴ Maintenance treatments include inhaled corticosteroids, long-acting beta agonists, leukotriene modifiers, methylxanthine, cromolyn (a mast-cell stabilizer), and immunomodulators. Reslizumab injection for intravenous (IV) use (Cinqair, Teva Pharmaceuticals), an interleukin (IL)-5 antagonist monoclonal antibody, is the newest maintenance immunomodulator approved by the Food and Drug Administration (FDA) in 2016.⁵

INDICATION

Reslizumab is indicated for patients 18 years of age and older as an add-on maintenance treatment of severe asthma with an eosinophilic phenotype. Reslizumab is not indicated for use in other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.⁵

Eosinophilic asthma is a subcategory of the disease characterized by the increased infiltration of eosinophils in the airway and presence in the sputum. The distinction of an asthma phenotype allows for more targeted therapies that offer more precise management of the condition. Eosinophilic asthma typically responds well to treatment with corticosteroids and T-helper type-2 targeted therapy, including anti-IL-5 agents.⁶

DOSAGE AND ADMINISTRATION⁵

Reslizumab is available as a solution in 100-mg/10-mL (10 mg/mL) single-use vials. It ranges in appearance from clear to slightly opaque and colorless to slightly yellow. Reslizumab is composed

of a protein and may appear as translucent or clear amorphous particles in the solution. Do not administer if foreign particles or discoloration is present. To minimize foaming, do not shake the vial or the prepared IV bag. Reslizumab is for IV infusion only and cannot be administered via bolus or IV push. The infusion must be prepared by a health care professional using aseptic technique and administered in a health care facility by a professional capable of managing anaphylaxis.

Dosing of reslizumab is based on patient weight at 3 mg/kg once every four weeks via IV infusion over 20–50 minutes. The infusion period is dependent on the total volume to be infused and patient weight. The volume corresponding to the appropriate weight-based dose is withdrawn in a syringe and then must be injected slowly into a 50-mL bag of 0.9% sodium chloride. Polyvinylchloride and polyolefin bags are compatible with reslizumab. The remaining unused reslizumab in the vial must be discarded.

Administration is recommended immediately after preparation. If the infusion is not used immediately, it must be stored either under refrigeration between 2° C and 8° C or at room temperature up to 25° C for no more than 16 hours after preparation and must be protected from light. The infusion set must have an in-line, low protein-binding filter with a pore size of 0.2 microns. Reslizumab is compatible with in-line infusion filters consisting of polyethersulfone, polyvinylidene fluoride, nylon, and cellulose acetate. The IV line used for reslizumab administration must not be used for any other agents, as physical and biochemical compatibility studies have not been conducted. Patients must be observed during and after the infusion for anaphylaxis for a clinically appropriate amount of time. In clinical trials, anaphylaxis was observed within 20 minutes of infusion and was reported as early as the second dose.

Table 1 Classification of Asthma⁴

Components of Severity		Asthma Severity			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤ 2 days per week	> 2 days per week, but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2 times per month	3–4 times per month	More than once per week, but not nightly	Often; 7 times per week
	Short-acting beta agonist use for symptom control	≤ 2 days per week	> 2 days per week, but not more than once per day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
	Lung function*	FEV ₁ > 80% predicted FEV ₁ /FVC normal Normal FEV ₁ between exacerbations	FEV ₁ ≥ 80% predicted FEV ₁ /FVC normal	FEV ₁ > 60% but < 80% predicted FEV ₁ /FVC reduced by up to 5%	FEV ₁ < 60% predicted FEV ₁ /FVC reduced by more than 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1 per year	2 or more per year		

FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity.
 * Normal FEV₁/FVC ratio for ages 8–19 years = 85%; ages 20–39 years = 80%; ages 40–59 years = 75%; ages 60–80 years = 70%.

Table 2 Stepwise Approach to the Management of Asthma⁴

Asthma Severity	Step	Medication	
		Preferred	Alternative
Intermittent	1	Short-acting beta agonist as needed*	None
Persistent	2	Low-dose inhaled corticosteroid	Cromolyn; leukotriene receptor agonist; nedocromil; or theophylline
	3	Low-dose inhaled corticosteroid AND long-acting beta agonist OR Medium-dose inhaled corticosteroid	Low-dose inhaled corticosteroid AND one of the following: • Leukotriene receptor agonist • Theophylline • Zileuton
	4	Medium-dose inhaled corticosteroid AND long-acting beta agonist	Medium-dose inhaled corticosteroid AND one of the following: • Leukotriene receptor agonist • Theophylline • Zileuton
	5	High-dose inhaled corticosteroid AND long-acting beta agonist	Consider omalizumab (Xolair, Genentech) in patients with allergies
	6	High-dose inhaled corticosteroid AND long-acting beta agonist AND oral corticosteroid	

* Short-acting beta agonists are used for symptomatic relief for all patients.

CLINICAL PHARMACOLOGY⁵

Mechanism of Action

Reslizumab is an IL-5 antagonist (immunoglobulin G4-kappa). IL-5 is a major cytokine involved in the growth, differentiation, recruitment, activation, and survival of eosinophils. IL-5 receptors

are expressed on the eosinophil surface. Reslizumab binds to the alpha chain of the IL-5 receptor on the eosinophil surface to inhibit the proliferation of eosinophils. The progression of inflammation is believed to contribute to the pathogenesis of asthma. Through inhibition of eosino-

phil production and survival, the inflammatory process of asthma is theoretically diminished.

Pharmacodynamics

Blood eosinophil counts were measured in clinical studies of reslizumab

administered at a dosage of 3 mg/kg. Mean eosinophil counts were recorded after the first dose and throughout 52 weeks of treatment. By week 52, patients receiving reslizumab showed a 92% reduction in mean eosinophil counts, compared with a 21% reduction in patients given placebo. No tachyphylaxis was observed during treatment. Eosinophil counts returned to baseline in patients who completed a 90-day follow-up, approximately 120 days after the last dose of reslizumab.

Pharmacokinetics

Absorption

Peak serum concentrations of reslizumab are often observed at the end of the infusion. The serum concentration declines in a biphasic manner. Serum concentrations accumulate with multiple dose administrations.

Distribution

Volume of distribution for reslizumab is 5 L, indicating a minimal distribution to the extravascular tissue.

Metabolism

Reslizumab, like other monoclonal antibodies, is metabolized by enzymatic proteolysis into small peptides and amino acids. Reslizumab is not expected to have a target-mediated clearance.

Elimination

Reslizumab is cleared at about 7 mL per hour and has a half-life of 24 days.

Special Populations

Population analysis demonstrated no significant differences in the pharmacokinetics of reslizumab with regard to age, race, and gender. No clinical studies have been conducted to assess the effect of renal impairment or hepatic impairment on the pharmacokinetics of reslizumab. However, population pharmacokinetic analysis suggested that no differences are seen in patients with normal or mildly increased liver function tests. In addition, no significant differences were observed among patients with normal renal function, mild renal impairment, or moderate renal impairment.

CONTRAINDICATIONS⁵

Contraindications include hypersensitivity to reslizumab or excipients.

WARNINGS AND PRECAUTIONS⁵

Boxed Warning: Anaphylaxis

After administration of reslizumab, patients must be observed for an appropriate period of time to treat potential anaphylaxis reaction. If anaphylaxis occurs, reslizumab must be discontinued immediately, and appropriate medical treatment must be given. Prior to discharge, the patient must be educated on the signs and symptoms of anaphylaxis and given instructions to seek immediate medical attention if symptoms occur. Reslizumab must be discontinued permanently if a patient experiences signs or symptoms of anaphylaxis.

Acute Asthma Symptoms or Deteriorating Disease

Reslizumab is not approved to treat acute asthma symptoms or acute exacerbations. Do not use reslizumab to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their symptoms worsen or remain uncontrolled while taking reslizumab.

Reduction of Corticosteroid Dosage

No clinical studies have been performed to assess the reduction of maintenance corticosteroids after the administration of reslizumab. Oral or inhaled corticosteroids must be tapered, if appropriate. Abrupt discontinuation of maintenance corticosteroid treatment for asthma may cause withdrawal symptoms or worsen asthma control. Do not abruptly discontinue corticosteroids upon administration of reslizumab.

Parasitic (Helminth) Infections

Eosinophils may be involved in the immunological response to certain parasitic infections. Patients with known parasitic infections were excluded in clinical trials. It is unknown if reslizumab affects the immune response against parasites. Pre-existing parasitic infections should be treated prior to initiation of reslizumab. If patients become infected with a parasitic infection while on reslizumab, discontinue treatment until the infection is resolved.

Adverse Reactions

The most serious adverse reactions to reslizumab included anaphylaxis and malignancies. Approximately 0.3% of patients reported anaphylaxis. These

events occurred within 20 minutes of the infusion as early as the second dose. Placebo-controlled clinical studies demonstrated that 0.6% of patients receiving 3 mg/kg of reslizumab developed at least one malignant neoplasm. In the placebo group, 0.3% of patients developed at least one malignant neoplasm. The malignancies observed in the reslizumab-treated patients were diverse in nature and without clustering of a particular tissue type. Most patients were diagnosed within six months of their exposure to reslizumab. Other reslizumab adverse reactions that occurred at a 2% incidence or greater and more often than with placebo included oropharyngeal pain. During clinical trials, patients randomized to reslizumab had elevated baseline creatine phosphokinase (CPK) levels compared with patients receiving placebo (14% versus 9%, respectively). Transient CPK elevation was reportedly higher in patients receiving reslizumab compared with those receiving placebo (20% versus 18%). CPK elevations greater than 10 times the upper limit of normal were reported in 0.8% of the reslizumab group and in 0.4% of the placebo group; however, these elevations were asymptomatic and did not result in treatment discontinuation. Myalgia was reported in 1% of the reslizumab group and in 0.5% of the placebo group. Musculoskeletal adverse events, including chest pain, neck pain, muscle spasms, extremity pain, and muscle fatigue, were reported on the day of infusion in 2.2% of reslizumab-treated patients and in 1.5% of those who received placebo.

Drug-Drug Interactions

No formal clinical drug interaction studies have been performed with reslizumab. Population pharmacokinetic analyses indicate that the simultaneous use of leukotriene antagonists or corticosteroids does not affect the pharmacokinetics of reslizumab.

USE IN SPECIAL POPULATIONS⁵

Pregnancy and Lactation

Data from clinical trials regarding exposure to reslizumab during pregnancy are insufficient to provide information on drug-associated risks. It is known that monoclonal antibodies are able to cross the placenta. There is potential for adverse effects on the fetus, particularly

during the second and third trimesters. The long half-life of reslizumab may also increase the risk of fetal adverse effects.

Pregnant mice and rabbits were exposed to IV reslizumab at six times and 17 times the maximum recommended human dose, respectively. These animal reproduction studies did not show evidence of adverse embryo-fetal developmental effects.

Women with poorly or moderately controlled asthma may have increased risk for preeclampsia, infants with low birth weight, and smaller neonates. Asthma control must be closely monitored in pregnant women to prevent risk to the fetus.

The presence of reslizumab in human milk is unknown, as is its effect on breastfed infants and on milk production. Lactating mice receiving reslizumab at 10 or 50 mg/kg (1.5 and 6.0 times greater, respectively, than the maximum recommended human dose) demonstrated excretion of reslizumab in milk. The levels of reslizumab were approximately 5% to 7% of the maternal serum reslizumab concentration.

Pediatric Patients

Reslizumab is not indicated for use in patients younger than 18 years of age. Safety and efficacy have not been established in this population. Clinical studies that evaluated 39 patients 12 years of age to less than 18 years of age demonstrated a higher exacerbation rate for adolescents treated with reslizumab compared with placebo.

Geriatric Patients

Two 52-week exacerbation studies and two 16-week lung function studies were performed in 122 patients 65 years of age and older with asthma. There were no significant differences in safety and effectiveness in older patients compared with younger patients. According to the available data, no dose adjustments are required for the use of reslizumab in the geriatric population.

CLINICAL TRIALS

Four randomized, double-blind, placebo-controlled studies were conducted with patients 12 years of age and older. Patients received reslizumab 3 mg/kg or placebo once every four weeks for 16 to 52 weeks. All patients

continued their background asthma regimen during the studies.⁵

Studies I and II^{5,7,8}

Studies I and II included 953 patients with eosinophilic asthma and an eosinophil count of at least 400/mcL and at least one asthma exacerbation requiring corticosteroid use over the past 12 months. The two studies lasted 52 weeks and were conducted simultaneously from 2011 to 2014. The objective of these two trials was to evaluate the efficacy and safety of reslizumab in the reduction of asthma exacerbations. Maintenance oral corticosteroids, up to an equivalent of prednisone 10 mg, were permitted. Most patients were on a medium to high dose of an inhaled corticosteroid and a long-acting beta agonist at baseline. Reslizumab or placebo was administered via IV at 3 mg/kg every four weeks for a total of 13 doses.

The primary endpoint of these two studies was the frequency of asthma exacerbations, which were defined as a worsening of asthma based on one of two criteria. The first criterion was the need for and use of a systemic corticosteroid or increased use of an inhaled corticosteroid over three or more days. In patients already receiving corticosteroid treatment, a twofold increase over the course of three or more days was considered an asthma exacerbation. The second criterion measured the frequency of emergency treatment, defined as an unscheduled visit to a health care professional for nebulizer treatment, an emergency room visit for asthma treatment, or an asthma-related hospitalization. An additional primary endpoint in studies I and II examined the frequency of each criterion in patients receiving reslizumab.

The patients receiving reslizumab had lower rates of total asthma exacerbations compared with patients receiving placebo, with relative reductions (RRs) of 50% in study I and 41% in study II. Patients receiving reslizumab also reported fewer exacerbations requiring systemic corticosteroid use compared with patients receiving placebo, with RRs of 45% and 39% in studies I and II, respectively. The number of exacerbations resulting in hospitalizations or emergency room visits in patients receiving reslizumab had RRs of 66% and 69% in studies I and II, respectively, when compared with the placebo group.

Study III^{5,9}

Study III included 315 patients with eosinophilic asthma who had an eosinophil count of at least 400/mcL. Patients were divided into three reporting groups. Two groups received reslizumab, and one group received placebo. One reslizumab group received 3.0 mg/kg via IV every four weeks for a total of four doses over 16 weeks. The second reslizumab group received 0.3 mg/kg via IV every four weeks for a total of four doses over 16 weeks. The third group received IV placebo every four weeks for a total of four doses over a period of 16 weeks.

The objective of study III was to determine the efficacy of reslizumab 3.0 mg/kg and 0.3 mg/kg compared with placebo in improving lung function in patients with eosinophilic asthma. This study excluded patients who required oral corticosteroids for maintenance therapy. The primary endpoint measured the change in forced expiratory volume in one second (FEV₁) over 16 weeks. FEV₁ measurements were taken at baseline and at weeks 4, 8, 12, and 16. The average of the FEV₁ measurements was estimated using a mixed-effect model for repeated measurements, with a positive change demonstrating improved asthma control. After 16 weeks, compared to baseline, FEV₁ improvements of 0.286 L and 0.242 L were reported in the reslizumab 3.0 mg/kg and 0.3 mg/kg groups, respectively, while the placebo group demonstrated an FEV₁ change of 0.126 L.

The mean changes in FEV₁ were compared between placebo and each of the reslizumab groups. The reslizumab 3.0 mg/kg group demonstrated an FEV₁ change 0.160 L greater than placebo (95% confidence interval [CI], 0.060–0.258; *P* = 0.0018). The reslizumab 0.3 mg/kg group demonstrated an FEV₁ change 0.116 L greater than placebo (95% CI, 0.016–0.215; *P* = 0.0237). Although two doses were studied, only the 3 mg/kg dose is currently approved by the FDA.

Study IV^{5,10}

Study IV included 497 patients with eosinophilic asthma. Patients were not included based on eosinophil counts. Approximately 80% of patients had an eosinophil count less than 400 mg/mcL. The objective of this study was to determine the efficacy of reslizumab 3 mg/kg

in improving the pulmonary function of patients with moderate-to-severe eosinophilic asthma. Patients requiring oral corticosteroids were excluded from this study. Reslizumab 3 mg/kg was administered intravenously every four weeks for a total of four doses over 16 weeks. The original primary endpoint measured efficacy through FEV₁ changes over 16 weeks. Reslizumab 3 mg/kg demonstrated an average FEV₁ 0.076 L greater than placebo (95% CI, -0.006 to 0.158; *P* = 0.076). The updated and current primary outcome measure evaluates FEV₁, measured in liters, in relationship to baseline eosinophil count, measured in 10⁹/L. The reslizumab 3.0 mg/kg group demonstrated an FEV₁ change of 0.0229 L/eosinophil 10⁹/L while placebo demonstrated an FEV₁ change of -0.2778 L/eosinophil 10⁹/L.

P&T COMMITTEE CONSIDERATIONS

Reslizumab is available in single-use 100-mg/10-mL (10 mg/mL) vials and is dosed via IV based on patient weight (3 mg/kg). It is approved for patients 18 years of age and older.⁵ The average wholesale price (AWP) for one vial is \$1,032. A hypothetical patient weighing 90 kg would need a monthly dose of 270 mg, which would require the contents of three vials at a total cost of \$3,096 (with the excess drug discarded).¹¹ Reslizumab carries a boxed warning for anaphylaxis; therefore, patients will require drug administration and subsequent observation by a health care professional who is able to treat an anaphylactic reaction. Malignancies and CPK elevation have also been reported with the use of reslizumab.⁵

Mepolizumab (Nucala, GlaxoSmithKline), an IL-5 antagonist monoclonal antibody approved in 2015, is also indicated for the treatment of severe asthma with an eosinophilic phenotype. Unlike reslizumab, mepolizumab may be used in adolescents as young as 12 years of age. The treatment is administered subcutaneously at a dosage of 100 mg every four weeks.¹² The AWP for a single-dose 100-mg vial is \$3,342.¹¹ Herpes zoster infections have been reported with the use of mepolizumab,¹² which is of particular concern for immunocompromised patients who are at increased risk of infections and do not qualify for the herpes zoster vaccination.

Omalizumab (Xolair, Genentech) is another immunomodulator that is FDA-approved for the treatment of asthma. However, omalizumab targets mast cells and basophils, not the eosinophils that exacerbate inflammation in a patient with eosinophilic asthma; therefore, it should not be considered as a treatment option for these patients.¹³

CONCLUSION

Reslizumab may benefit patients 18 years and older who have uncontrolled eosinophilic asthma even while receiving corticosteroid treatment by reducing the frequency and severity of asthma exacerbations. Immunocompromised patients with severe asthma who are unable to receive a herpes zoster vaccination and as a result have a greater risk for infection may also benefit from reslizumab.

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