



Mepolizumab's (Anti-Interleukin-5) Role in Severe Asthma: A Literature Review

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Abstract

One type of asthma that is difficult to treat is severe asthma, which is asthma that is uncontrolled even when the patient is taking medication or trigger factors. It can be treated with the finest therapy but will worsen if high-dose treatment is discontinued. Age, gender, obesity, hypersensitivity, and immunological factors are all directly related to the onset of asthma. A complicated illness, severe asthma has many clinical symptoms and treatment choices. Chronic airway inflammation and lung tissue remodeling are its defining features. This literature review aims to describe how mepolizumab works in patients with severe asthma. Mepolizumab mainly inhibits the IL-5 cytokine from binding to IL-5 receptor subunits through the nanomolar potential, which inhibits IL-5 from binding to receptors on the surface of eosinophils. In contrast to the placebo group, patients on mepolizumab had an average 50% decrease from the baseline Prednisone dosage. With Mepolizumab, the yearly exacerbation rate was 1.44 RR, while it was 2.12 RR with placebo. The injection of monoclonal antibodies, such as mepolizumab, as a form of therapy in addition to treating severe eosinophilic asthma is advised by the GINA guideline for 2022. Mepolizumab's mode of action blocks IL-5 from binding to receptors on eosinophil surfaces, which lowers eosinophil recruitment, activation, production, growth, and survival, as well as eosinophil-mediated inflammation.

Keywords: eosinophil, interleukin-5, mepolizumab, severe asthma

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INTRODUCTION

One form of difficult-to-treat asthma is severe asthma, which is asthma that is uncontrolled even when the patient is taking medication or trigger factors. It can be managed with the best therapy but will get worse if high-dose treatment is stopped.^{1,2} 'Severe asthma, which is related to higher mortality, morbidity, persistent daily symptoms, hospitalization, and health care cost issues, as well as lower patient quality of life, affects 5–10% of all asthma patients.^{3,4} Treatment costs for those with severe asthma are six times higher than those for people with mild and moderate asthma.⁵

Age, gender, obesity, hypersensitivity, and immunological variables directly impact asthma development. In 80% of kids over the age of 6, atopy is a risk factor for developing asthma.^{1,5,6}

According to research conducted in the Netherlands on asthma patients over the age of 18, 24% are receiving therapy according to steps four and five of the Global Initiative for Asthma (GINA)

management recommendations. The group of people with difficult-to-treat asthma makes up 17% of the population, while the group of people with severe asthma makes up 7.7% of the 17%.^{1,7} Chronic airway inflammation and lung tissue remodeling characterize the diverse illness known as severe asthma, which has a range of clinical symptoms and therapeutic responses.^{5,8,9}

Mepolizumab significantly reduced the frequency of exacerbations, the use of oral corticosteroids (OCS), hospitalization, and emergency room visits in Shabbir *et al.*'s study of the drug as an adjunctive therapy for severe eosinophilic asthma when compared to placebo.^{10,11}

Knowledge of the pathobiology of asthma helps select the appropriate target group and predict biomarkers as an indication for administering mepolizumab in the therapy of severe asthma.¹² This literature review aims to describe mepolizumab's function in treating individuals with severe asthma.

PHENOTYPES, ENDOTYPES, AND BIOMARKERS OF SEVERE ASTHMA

According to GINA 2022, severe asthma is uncontrolled asthma even if the patient has had the best care possible, including high doses of Inhalation Corticosteroid-Long-Acting-Beta-Agonist (ICS-LABA) and the best management of precipitating events, or if asthma gets worse if high-dose treatment is discontinued. Correct inhaler use techniques, poor patient compliance, comorbidities (gastroesophageal reflux diseases, chronic rhinosinusitis, obstructive sleep apnea), precipitating factors, living or working environment (smoking, exposure to environment and allergens), frequent use of short-acting beta-agonist (SABA) reliever drugs, side effects of drugs, anxiety, and depression are some of the factors that contribute to symptoms, exacerbations.^{1,3,5}

If the causes underlying the asthma have dramatically improved after 3 to 6 months of appropriate medication, severe asthma is not considered.¹ In comparison to mild to moderate asthma, severe asthma is associated with higher rates of morbidity, more frequent exacerbations, a higher risk of death, drug use, doctor visits, hospitalizations, OCS side effects, and health care costs that are six times higher.¹

According to research done in England, people with severe asthma have higher healthcare costs than people with type 2 diabetes mellitus, stroke, and chronic obstructive pulmonary disease. Canadian research indicates that those with severe asthma are projected to spend over 60% more on healthcare than people with mild to moderate asthma.¹

In the Netherlands, a study on asthma patients over the age of 18 found that approximately 24 percent of the population was being treated by steps four and five of the GINA management guidelines, 17% of the population belonged to the group of patients with difficult-to-treat asthma, and approximately 3.7% of these patients had an asthma attack. The Asthma Control Test (ACT) assessment, adherence, and inhaler technique were used to determine the number of patients treated with high-dose ICS-LABA or moderate/high-dose ICS-LABA + long-term OCS with

poor symptom control.⁵ Asthma affects between 0.2 and 21% of persons worldwide. There are wide variations in the reported prevalence of severe asthma.^{3,9,13} In between 5 and 10% of persons, according to research by Miyokawa et al., suffer severe or hard-to-treat asthma.⁵

Chronic airway inflammation and lung tissue remodeling are hallmarks of the complicated illness known as severe asthma, which has a range of clinical symptoms and treatment effects. The molecular phenotypic, endotypic, biomarker, and treatment response variability of asthma is on the rise. The main criterion for categorizing asthma is the presence of an eosinophilic inflammatory process that is T-helper 2 (Th-2). To optimize the use of specialized therapy, it is essential to establish the phenotypes, endotypes, and biomarkers of severe asthma (Figure 1).⁵

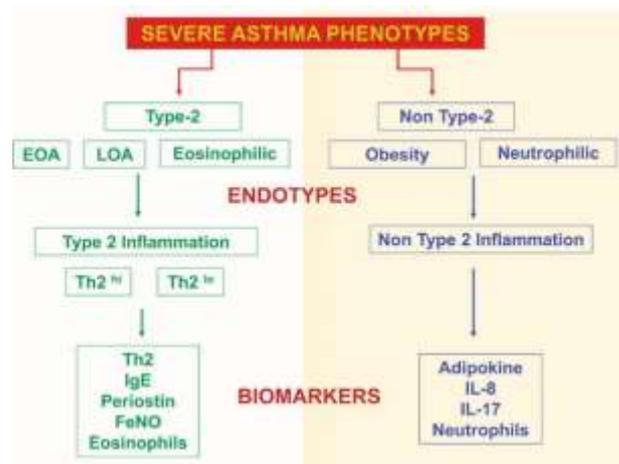


Figure 1. Phenotypes, endotypes, and biomarkers of severe asthma⁵

Severe Asthma Phenotype

The manifestation of a patient's characteristics, or phenotype, may be seen and made explicit through interactions between the patient's environment and genotype, such as lung function and Immunoglobulin (IgE) (biomarker) responses to specific allergens. Based on a combination of physiological, biochemical, and clinical traits. In a literature review, Noujeim et al. organized the phenotypes of people with severe asthma.^{5,7}

These characteristics are divided into two groups: the inflammatory and clinical phenotypes. Severe asthma with recurring exacerbations, asthma

with fixed airflow restriction (irreversible airway obstruction), and asthma needing systemic corticosteroids as therapy are the three clinical phenotypes. The two kinds of inflammation that make up the three phenotypes and paucigranulocytic (neutrophil eosinophil value normal) are chronic severe eosinophilic asthma (Eosinophil value >3%) and severe neutrophilic asthma (neutrophil value >61%), as illustrated in Table 1.^{5,7}

Table 1. Characteristics of the severe asthma phenotype⁷

Clinical phenotype	Inflammatory phenotype
Severe asthma with frequent exacerbations	Persistent severe eosinophilic asthma
Asthma with obstruction-fixed <i>airflow</i>	Non-eosinophilic severe asthma with increased neutrophils
Corticosteroid dependent asthma	Paucigranulocytic severe asthma

Severe asthma of the type 2 and non-type 2 phenotypes were identified by Piuvezam et al. The Th2 immune response was used to identify a unique type 2 severe asthma phenotype to indicate severe asthma type 2. Elevated CD4+ T cells are seen in bronchoalveolar fluid, mucosal biopsies, blood eosinophils, airway eosinophils, and high serum titers of allergen-specific IgE. The eosinophilic asthma, late-onset, and early-onset asthma subtypes are the three subgroups of the severe asthma type -2 phenotype. When EOA, or allergic asthma, is linked to a family history of allergies, such as eczema, allergic rhinitis, food allergies, and medication allergies, it often manifests in children as the most easily identifiable phenotype.^{5,6,14}

Some young children with early-onset asthma react effectively to corticosteroids and have reduced IgE levels. The EOA phenotype is significantly influenced by age. Compared to individuals with other phenotypes, pediatric patients with an early beginning of the severe atopic phenotype have a worse prognosis.^{5,6,14}

Adult-onset asthma, also known as late-onset asthma (LOA), is a condition that develops beyond the age of 65 and affects 8 – 10% of people. Most adult asthma patients, particularly women, initially develop asthma in adulthood. At 65 years of age,

LOA patients have a 4–15% higher morbidity and mortality rate than young adults.^{1,5,6}

Since late-onset asthma usually has no prior history of allergies, high-dose corticosteroid therapy is necessary. One of the most prevalent forms of LOA in modern nations is occupational asthma. Nasal polyps and sinusitis are frequently seen in adult-onset asthma with very high eosinophil levels. This phenotype demonstrates a connection between mast cells and basophils, two types of inflammatory cells, and type 2 cytokines.^{5,6,15}

In severe asthma, eosinophils are associated eosinophils, which are granulocytic cells known as effector cells that produce and keep biologically active molecules, including cytotoxic proteins, namely major essential protein (MBP), eosinophil peroxidase (EPX), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), mediators—Lipids, chemotactic peptides and other cytokines functional toward pathogens. Eosinophil granule protein is toxic to pathogens and other cells during an immune response, resulting in tissue damage and organ failure. Eosinophils create and expel a large number of proinflammatory cytokines and chemokines.^{1,5,6,13}

Patients with non-type 2 severe asthma phenotypes frequently have obesity asthma and neutrophilic asthma. Obese asthmatic patients with the EOA phenotype had more bronchial hyperreactivity, a history of atopy, more significant airway obstruction, higher serum IgE levels, and a higher risk of sensitization and allergic reactions than obese asthmatics with the LOA phenotype. In contrast to the predominance of severe asthma, while being treated with corticosteroids, neutrophilic asthma is related to neutrophils because they are not linked to airway hyperreactivity.^{1,5,6} Clinical phenotypes of asthma include allergic, nonallergic, adult-onset (late-onset), chronic airflow limitation, and obese asthma, according to GINA 2022.¹

Endotype of Severe Asthma

Based on airway immune-mediated inflammation, type 2 (T2-high asthma) and non-type

2 (T2-low asthma) inflammatory responses are two endotypes of severe asthma (Figure 2).^{5,6}

Type 2 inflammation is a complex form of inflammation encompassing innate and adaptive immune responses, asthma risk factors, allergy processes, and other inflammations. After allergens have already harmed these cells, dendritic cells activate airway epithelial cells. Chemokines, chemotactic inflammatory mediators produced by epithelial cells, attract dendritic cells to the mucosal epithelium. Mature dendritic cells recognize allergens, present them to T cells via MHC classes I and II for T cell receptor recognition, and cause the activation of Th2 cells as antigen-presenting cells (APC).^{5,6}

When Th2 cells activate IL-5, they also produce eosinophils. Once TGF- is made by these eosinophils, fibroblasts are activated, and the smooth muscles of the airways are contracted. Additionally, fibroblasts are stimulated by the IL-4 and IL-13 produced by Th2 cells. Mast cells stimulate Th2 cells, and Th2 cells stimulate B cells to create IgE, constricting the smooth muscle of the airways. Proinflammatory cytokines and chemokines are produced and excreted in part by eosinophils. Nitric oxide (FeNO), higher serum periostin levels when there are more eosinophils in the sputum, poor asthma control, and a severe disease profile can all be used to predict severe eosinophilic asthma. On a fundamental level, what generates the rise in FeNO is still unknown. Airway fibroblasts and epithelial cells release Periostin in response to the type 2 cytokines TGF and IL-4/IL-13.^{1,5,6}

Additionally, substances, cigarette smoke, and lipopolysaccharides (microorganisms) that cause non-type 2 inflammation are activated, as well as the innate immune system, Th1 and Th17 inflammatory pathways.^{5,6} IL-8 production, non-type 2 inflammation, high-affinity IgE receptor expression, and increased neutrophils in the bronchi. Chemotactic cytokines (IL-8 and TNF-), secreted by neutrophils, macrophages, and epithelial cells, impact the quantity of neutrophils in the airways. Neutrophils are attracted to IL-17 produced by T cells. Airway remodeling brought on by increased mucus production, airway smooth muscle hyperplasia/hypertrophy, and goblet cell

metaplasia/hyperplasia defines non-type 2 asthma. Non-type 2 asthma also functions in neutrophil or paucigranulocytic inflammation, producing IL-8 and IL-17.^{5,6}

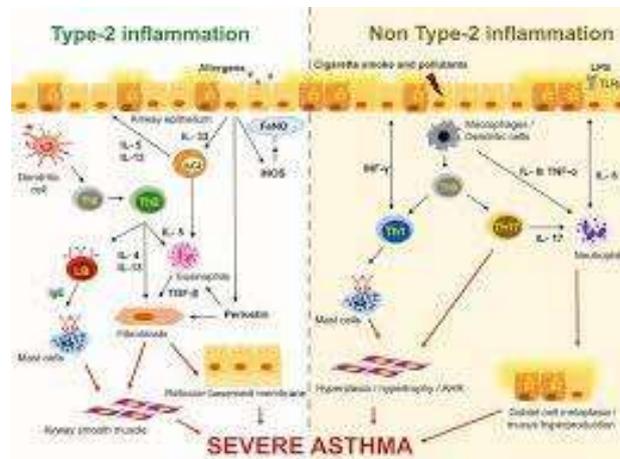


Figure 2. Type 2 inflammation and non-type 2 inflammation in severe asthma⁵

Severe Asthma Biomarkers

A biomarker is an indicator that links phenotype and endotype. Indicators can be measured and evaluated using various biological materials, including sputum, bronchoalveolar lavage (BAL), exhaled breath condensate (EBC), bronchial biopsies, urine, and blood. The effectiveness of various therapy approaches may be evaluated using biomarkers, as can the chance that a disease would emerge and the distinction between type 2 and non-type 2 inflammatory endotypes. Additionally, they can be used to predict how patients will respond to particular therapies, such as T2 cytokine-targeted therapy. The biomarkers for asthma are grouped by sample in Table 2.¹⁴

Inflammation and asthma remodeling are assessed through bronchoscopy, bronchial biopsy, and BAL examination. For the evaluation of asthma, particularly in patients with severe asthma, biomarkers alone or in combination are recommended. The presence of periostin, FeNO, serum IgE, and blood or sputum eosinophils can detect type 2 inflammation. A poor response to corticosteroid treatment and neutrophilic (sputum neutrophils >40–60%) or paucigranulocytic (sputum eosinophils and neutrophils normal) inflammation are

characteristics of non-type 2 inflammation. The ability of neutrophils, a non-type 2 inflammatory biomarker, to predict asthma severity and anti-inflammatory mechanisms is limited.¹⁴

Table 2. Characteristics of the severe asthma biomarkers¹⁶

Biomarker	Sample type	Associated asthma endotypes
Eosinophils	Serum, sputum	Type-2
Neutrophils	Sputum	Type-2/non-type-2
IgE	Serum	Type-2
Periostin	Serum	Type-2
FeNO	Exhaled air	Type-2
IL-17	Serum	not type-2
EBC	Exhaled air	Not specified
VOCs	Exhaled air	Not specified

Note: FeNO=fractional exhaled nitric oxide; EBC=exhaled breath condensate; VOCs=volatile organic compounds

SELECTION OF SEVERE ASTHMA TREATMENT

The GINA 2022 recommendations for treating severe asthma include using a high-dose ICS-LABA combination for 3–6 months and optimizing the treatment of steps 4–5. Reasonable asthma control cannot be achieved with the use of a medium-dose ICS plus LABA, and a third controller (LTRA or theophylline). a LAMA (long-acting muscarinic antagonist), either alone or combined with a medium-dose ICS-LABA or Zithromax, thrice weekly.

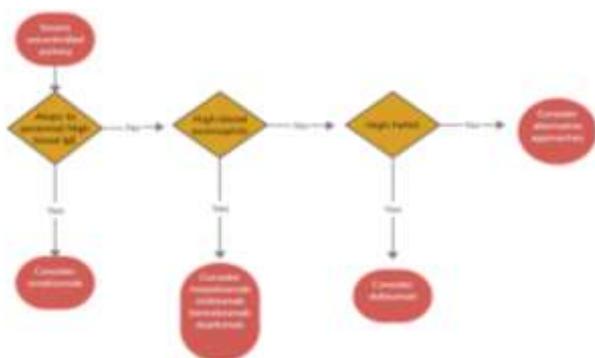


Figure 3. Algorithm for selection of biologic treatment for severe asthma²

Clinical biomarkers and patient-focused asthma endotypes should be considered while providing supplementary biologic treatment to persons with severe asthma. If you have severe allergic asthma and high IgE levels, you might think about further anti-IgE therapy (omalizumab). Mepolizumab, reslizumab, and bevacizumab are additional anti-IL-5/IL-5 receptor drugs for persons

with severe asthma and elevated blood eosinophil levels. The administration of daclizumab, an additional anti-IL-4R drug, results in greater levels of FeNO when using the strategy shown in Figure 3 to select an empiric biologic therapy for severe asthma.¹

MEPOLIZUMAB (ANTI INTERLEUKIN-5) MECHANISM OF ACTION AND CLINICAL USE

To stop IL-5 from attaching to receptors on the surface of eosinophils, mepolizumab precisely prevents IL-5 cytokine binding to IL-5 receptor subunits via the nanomolar potential (Figure 4). Interleukin-5 is the main cytokine in eosinophil synthesis, differentiation, migration, activation, and survival. Anti-IL-5's capacity to inhibit eosinophil recruitment, activation, generation, growth, and survival reduces eosinophil-mediated inflammation. In just 24 hours, mepolizumab therapy can reduce blood eosinophil levels by up to 50%.^{13,15}

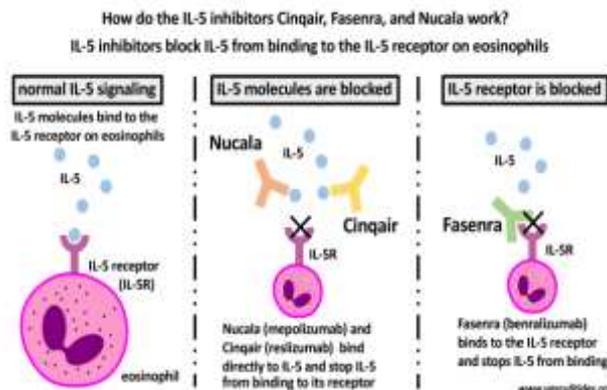


Figure 4. Mepolizumab mechanism of action

In patients receiving high-dose inhaled corticosteroids along with one or more controllers, such as LABA, mepolizumab is used to treat severe persistent asthma in adults, adolescents, and children aged six years and older with an eosinophil count of 150 cells/L at the beginning of treatment or 300 cells/L in the previous 12 months. Mepolizumab and a placebo were evaluated in eight studies by the Cochrane Airways Group, involving 1707 participants, and in one randomized research with 621 individuals, administration of mepolizumab 75 mg, 250 mg, or 750 mg at four-week intervals led to eosinophilic inflammation. Blood eosinophil levels significantly dropped among mepolizumab users.¹⁷

Mepolizumab significantly decreased the annual number of exacerbations compared to placebo in a study that included 806 asthma patients who had exacerbations while receiving OCS treatment - a 48% decrease at a dosage of 75 mg. Patients with severe eosinophilic asthma who had gone through two exacerbations in the previous year were given mepolizumab 100 mg subcutaneously. When compared to those who took a placebo, 194 of the 449 patients who experienced exacerbations reported a reduction in exacerbations of 1.74 relative risk (RR) or 0.83.¹⁷

In a study, mepolizumab was administered subcutaneously to 135 patients with severe eosinophilic asthma who had been on 5–35 mg of prednisone for six months. The patients were assessed 20 weeks after getting mepolizumab or a placebo while still taking corticosteroids. The trial's findings demonstrated that mepolizumab users saw an average 50% reduction in Prednisone dosage from the starting dose, while the placebo group did not see a corresponding drop. With mepolizumab, the yearly exacerbation rate was 1.44 RR as opposed to 2.12 RR with a placebo.¹⁷

Pharmacodynamics of Mepolizumab

In a study by Russell et al., mepolizumab was given subcutaneously at a dose of 100 mg once every four weeks to patients with severe eosinophilic asthma in both adults and adolescents. This treatment was more effective than a placebo in lowering blood eosinophil levels, which decreased from an initial average of 290 cells/L to 40 cells/L in the sixth week. Between 4 weeks and 4.5 years, the average time for the blood eosinophil levels to decline was 2.8 years. Every four weeks for 52 weeks, children aged 6 to 11 years got mepolizumab subcutaneously. Blood eosinophil levels dropped further after the 40 mg dosage (for a weight of 40 kg) than the baseline average of 306 cells/L, down to 48 cells/L after 52 weeks. These data demonstrate a decline of 85% and 87%, respectively, after the start of the treatment.¹⁸

Mepolizumab should be administered parenterally or intravenously to individuals with

eosinophilic asthma once every four weeks for 32 weeks and once every four weeks to patients with eosinophilic granulomatosis polyangiitis. Children under 12 receive the exact dosage as an adult, whereas children aged 6 to 11 receive 40 mg once every four weeks for 52 weeks.¹⁹

Mepolizumab comes in vials, prefilled syringes, and autoinjectors in 10 mL colorless translucent glass bottles with bromobutyl rubber (non-latex) covers aluminum top seals, and plastic flip tops. As many as 100 mg of powder for injectable solution is contained in each vial. Since a single-use bottle doesn't contain preservatives, reconstitution must be completed in an aseptic setting.¹⁹

Pharmacokinetics Mepolizumab

According to a study by Russell et al., we were treating patients with severe eosinophilic asthma with mepolizumab at a dose of 100 mg subcutaneously every four weeks reduced blood eosinophil levels compared to placebo administration, going from an initial average of 290 cells/L to 40 cells/L in the sixth week. Between 4 weeks and 4.5 years, this decrease in blood eosinophil levels lasted an average of 2.8 years. Every four weeks, for a total of 52 weeks, mepolizumab was administered subcutaneously to children aged 6 to 11 years.¹⁸

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Pharmacokinetics Mepolizumab

Patients with severe asthma receive subcutaneous injections of mepolizumab at a dosage ranging from 12.5 mg to 250 mg. T_{max}, which ranges from 4 to 8 days, measures the median time to maximum plasma concentration and shows that absorption is slow. After subcutaneous injection, Mepolizumab's absolute bioavailability was 64%, 71%, or 75% in the belly, z group exhibited decreased dependency on oral glucocorticoids, according to the data (OR=2.39; 95% CI=1.25–4.56; P=0.008). There was no difference in the percentage of mean reduction from baseline consumption of glucocorticoids by 50% between the Mepolizumab and the placebo groups. Both subcutaneous and intravenous administration of mepolizumab is equally beneficial in decreasing exacerbations, improving quality of life, and minimizing the requirement for oral glucocorticoids.²⁵

CONTRAINDICATIONS AND SIDE EFFECTS OF DRUGS

Special consideration should be given to patients who take steroids, have a history of parasitic worm infection or herpes zoster, are children, are pregnant, or are breastfeeding. Mepolizumab's primary contraindication is hypersensitivity to the medication's components. Adverse side effects were common and included headaches (19%), nasopharyngitis (18%), and hypersensitivity reactions (1–10%). Local reactions were seen at 38% of injection locations. The frequency of local symptoms, including soreness, edema, erythema, itching, and burning, subsided after the first three injections. Other common reactions include musculoskeletal problems like back pain or muscle spasms, skin diseases including pruritus and

dermatitis, and digestive system problems like stomach discomfort.¹⁷ Depending on the patient's evaluation cycle, response to therapy, risk of aggravation, and drug side effects decide how to treat asthma patients.¹

CONCLUSION

The 2022 GINA recommendations state that severe asthma remains uncontrolled despite optimal patient adherence to high-dose ICS-LABA and effective management of precipitating causes or worsening asthma when high-dose therapy is discontinued. The injection of monoclonal antibodies, such as mepolizumab, as a form of treatment in addition to treating severe eosinophilic asthma is advised by the GINA guideline for 2022. Mepolizumab's action method blocks IL-5 from binding to receptors on eosinophil surfaces, which lowers eosinophil recruitment, activation, production, growth, and survival, as well as eosinophil-mediated inflammation. Mepolizumab effectively improves quality of life, decreases the need for oral corticosteroids, and reduces the frequency of asthma attacks.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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