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Severe asthma and biologic therapies in children and adults

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Abstract:

Severe asthma is characterized by persistent symptoms or recurrent exacerbations despite appropriately delivered high-dose controller therapy, verified adherence, correct inhaler technique, and optimal management of comorbidities and relevant triggers, or by deterioration in control when treatment intensity is reduced. Although severe asthma affects only an estimated 3–10% of patients with asthma, it accounts for the majority of asthma-related morbidity and mortality. Biologic agents constitute an important treatment option for severe asthma, and responses to these therapies vary across endotypes, which are broadly classified as type 2–high or type 2–low. Approved biologic agents for asthma management target immunoglobulin E (IgE), interleukin-5 (IL-5), the interleukin-4 receptor (IL-4R), and thymic stromal lymphopoietin (TSLP). Selection of an appropriate biologic agent is guided by markers of type 2 inflammation, such as blood eosinophil counts, fractional exhaled nitric oxide (FeNO), and serum IgE levels. However, substantial overlap in clinical and inflammatory profiles among patients often complicates identification of the most suitable biologic therapy. This review synthesizes available data from randomized controlled trials and real-world studies evaluating the clinical efficacy of biologic agents in the current management of severe asthma and aims to provide a practical perspective by integrating key biomarkers into clinical decision-making.

Keywords:

Biologic therapies, biomarkers, endotype, severe asthma

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Introduction

Asthma is a chronic disorder characterized by persistent airway inflammation that can occur at any age and typically presents with symptoms such as cough, dyspnea, or chest tightness.[1] Symptom intensity varies over time, and airflow limitation may become persistent. Inhaled corticosteroids (ICS) remain the mainstay of asthma management, effectively reducing airway inflammation, improving symptom control, and preventing exacerbations. Difficult-to-treat asthma refers to asthma that remains uncontrolled despite treatment with medium- or high-dose ICS plus a second controller or maintenance oral corticosteroids (OCS), or that

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requires high-dose therapy to maintain symptom control and reduce exacerbations.[2] Inadequate asthma control may be associated with modifiable factors, including incorrect inhaler technique, poor treatment adherence, smoking, obesity, exposure to environmental or occupational allergens, or misdiagnosis.[1] In patients with suboptimal asthma control, the possibility of obstructive sleep apnea should be considered, and individuals should be evaluated accordingly.[3]

Low adherence to treatment is a key contributor to poor disease control in obstructive lung diseases. Suboptimal adherence may arise from incorrect use of inhaler devices, irregular use of controller medications, or limited perception of disease severity. Notably, during periods of heightened health threat, such as the coronavirus disease 2019 (COVID-19) pandemic, patients demonstrated temporary improvements in adherence, highlighting the critical role of patient education and illness awareness in optimizing asthma management.[4] Additionally, structured education on inhaler technique is of critical importance, and evidence indicates that training provided by physicians significantly improves inhaler use accuracy and associated clinical outcomes.[5] Although the type of inhaler device is often considered in clinical practice, recent evidence suggests that device selection alone does not substantially influence asthma outcomes.[6]

Severe asthma is defined as asthma that remains uncontrolled despite optimization of modifiable factors.[2] According to the Global Initiative for Asthma (GINA), severe asthma affects an estimated 3–10% of patients with asthma.[1] Among children with asthma, however, severe disease appears to be less common, with a reported prevalence of approximately 3%.[7] The prevalence of severe asthma varies substantially between countries. In a study conducted in the Netherlands, approximately 24% of adults with asthma required management at GINA Steps 4–5. Within the overall asthma population, an estimated 17% met the criteria for difficult-to-treat asthma, whereas a further 3.7% constituted the subgroup that remained uncontrolled despite documented good adherence and correct inhaler technique and were therefore classified as having severe asthma.[8] Severe asthma has been reported in 8.1% of patients with asthma in Denmark and 4.2% in Sweden.[9,10] These differences are attributed to heterogeneity in genetic and environmental factors. Additionally, the absence of a universally accepted and precise definition of asthma, along with the use of varying definitions and methodologies in epidemiological studies, complicates comparisons of prevalence data across studies.[1]

Endotypes of Asthma

Asthma can be broadly categorized into two major endotypes, each driven by distinct immunological pathways and exhibiting variable clinical responses to treatment.

Type 2 (T2)-High Endotype: Exposure to pollutants, viruses, or bacteria can render airway epithelial cells more fragile and increase their permeability to environmental factors, ultimately causing tissue injury.[11] As a result, epithelial cells secrete innate cytokines, referred to as alarmins, including thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and interleukin-33 (IL-33). Alarmins stimulate the differentiation of T helper 2 (Th2) cells and trigger activation of type 2 innate lymphoid cells (ILC2s). Both ILC2s and Th2 cells secrete several T2 cytokines, including interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). IL-4 and IL-13 promote class switching in allergen-specific B cells, leading to immunoglobulin E (IgE) production. IgE subsequently binds to high-affinity FcεRI receptors on mast cells and basophils. Allergen-induced cross-linking of surface-bound IgE triggers degranulation and the release of pro-inflammatory mediators.[12] IL-4 further induces IgE production by B cells, whereas IL-5 promotes eosinophil maturation and differentiation. IL-13 upregulates inducible nitric oxide synthase expression in airway epithelial cells, resulting in increased fractional exhaled nitric oxide (FeNO) levels, and contributes to mucus hypersecretion and airway hyperresponsiveness.[13] Airway remodeling initiated by alarmins requires the expression of fibrogenic and angiogenic factors, leading to marked structural alterations in the bronchial walls and blood vessels. These changes result in airway narrowing and stiffening, which clinically manifest as airflow limitation and respiratory symptoms.[14] Biologic therapies primarily target the T2-high endotype. The immunopathogenesis of T2-high severe asthma and the biologics targeting this pathway are illustrated in Figure 1.

T2-Low Endotype: T2-low asthma is characterized by increased disease severity, airway remodeling, and poor responsiveness to anti-inflammatory therapy. The immunopathogenesis of this endotype involves several mechanisms, including intrinsic neutrophil abnormali-

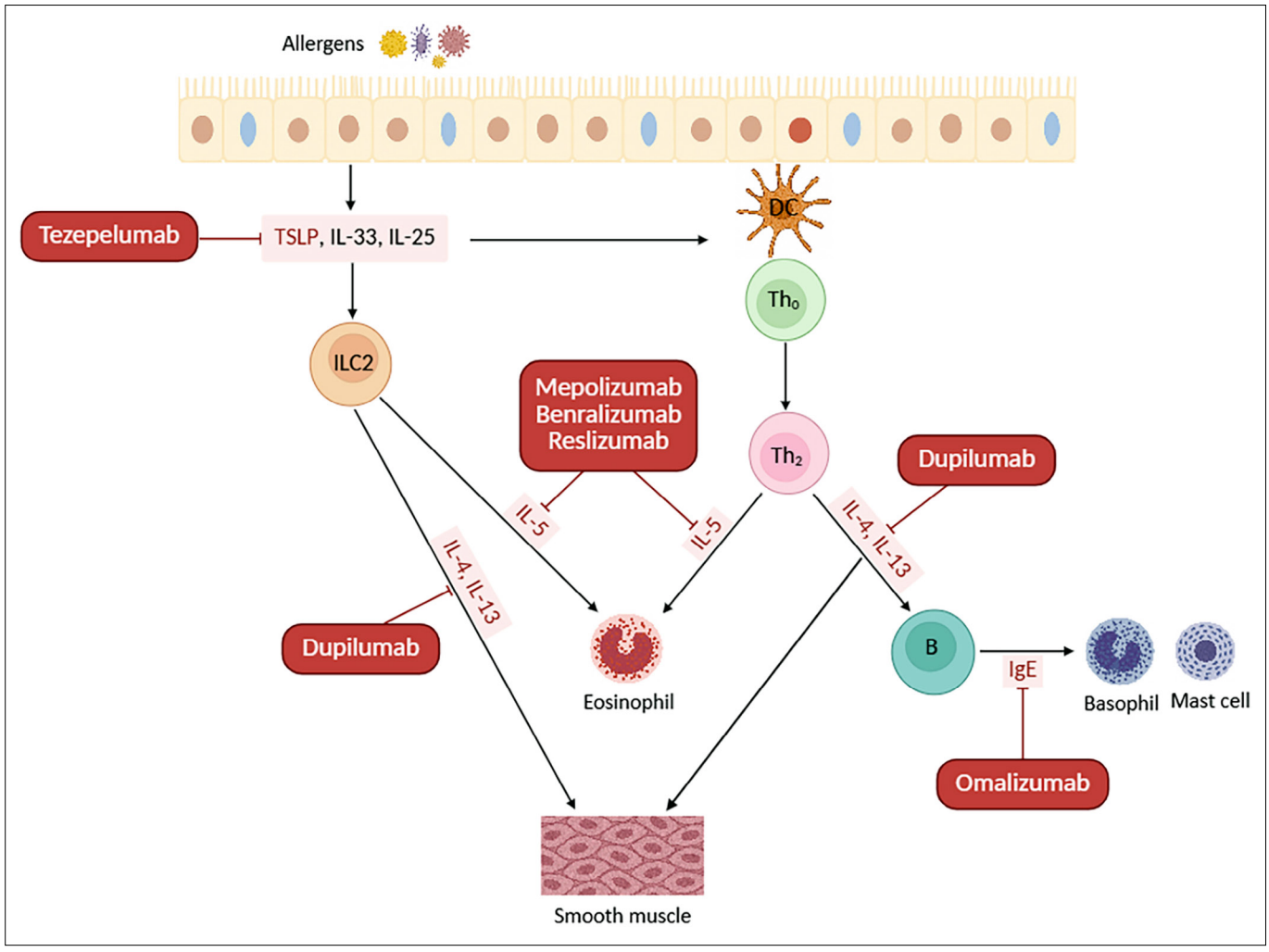

Figure 1: Type 2 (T2)-high severe asthma immunopathogenesis and specific biologic targets. In T2-high asthma, exposure to allergens, pollutants, or microbial agents stimulates the airway epithelium to release alarmins, including interleukin-33 (IL-33), IL-25, and thymic stromal lymphopoietin (TSLP). Dendritic cells (DCs) present these aeroallergens to naïve CD4+ T cells (Th0), promoting their differentiation into T helper 2 (Th2) cells. IL-4 is a critical cytokine driving this differentiation process. Activated Th2 cells, together with type 2 innate lymphoid cells (ILC2s), produce large amounts of type 2 cytokines, including IL-4, IL-5, and IL-13. In addition to promoting Th0-to-Th2 differentiation, IL-4 in combination with IL-13 plays a key role in inducing immunoglobulin E (IgE) class switching in B lymphocytes. IgE binds to the high-affinity FcεRI receptors expressed on mast cells and basophils. Upon re-exposure to the same allergen, cross-linking of these IgE molecules triggers the release of histamine, leukotrienes, and prostaglandins, leading to bronchoconstriction

ties, activation of inflammatory pathways, and engagement of the IL-17 axis.[14] Activation of T helper 1 (Th1) and T helper 17 (Th17) cells leads to elevated levels of interleukin-17A (IL-17A). Bronchial biopsies obtained from individuals with severe asthma demonstrated increased levels of Th17-associated cytokines, which mediate neutrophil recruitment to the airways.[15] Consequently, elevated IL-17 activity has been recognized as a distinct contributor to the development of severe asthma. T2-low asthma typically presents in adulthood and is frequently associated with factors such as obesity, aging, alterations in the lung microbiome, epithelial dysfunction, and gastroesophageal reflux disease.[11]

Biomarkers of Asthma Used in Clinical Practice

The ideal biomarker for asthma should accurately reflect the underlying pathophysiological mechanisms or therapeutic targets, exhibit high sensitivity and specificity, and be easily obtainable with minimal discomfort or risk. Additionally, it should be reproducible, cost-effective, practical, and safe, while providing valuable prognostic and pharmacodynamic information for disease monitoring.

Eosinophils

The extent of eosinophilic inflammation in blood and sputum correlated with disease activity in both atopic

and non-atopic asthma.[16] Blood eosinophil count (BEC) remains a valuable biomarker for differentiating asthma phenotypes and evaluating response to treatment.

Sputum eosinophils

Eosinophil counts in induced sputum provide valuable insight into asthma phenotypes and underlying disease mechanisms. A sputum eosinophil count of ≥2% suggests underlying eosinophilic airway inflammation.[1] Higher sputum eosinophil levels have been associated with an increased incidence of exacerbations and suboptimal disease control.[17]

Blood eosinophil count

An elevated BEC exceeding national or regional reference values may indicate type 2 asthma, although lower counts do not exclude this diagnosis. Blood eosinophil levels may also be elevated in non-asthmatic conditions, including parasitic infections, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis with nasal polyposis (CRSwNP), hypereosinophilic syndrome, and eosinophilic granulomatosis with polyangiitis (EGPA). In addition, BEC can be influenced by age, sex, timing of measurement (with afternoon values generally lower), geographic region, obesity, and atopy.[18] BEC ≥150/μL during treatment with high-dose ICS or maintenance OCS suggests the possibility of refractory type 2 inflammation.[1]

Fractional concentration of exhaled nitric oxide

Nitric oxide synthesis in airway epithelial cells is promoted by the cytokines IL-4 and IL-13. FeNO levels show a moderate correlation with sputum eosinophil counts and blood eosinophil levels and are typically elevated in type 2-high asthma.[19] FeNO may also be increased in non-asthmatic conditions, such as eosinophilic bronchitis, atopy, allergic rhinitis, and atopic dermatitis, while remaining normal in certain asthma phenotypes, including neutrophilic and obesity-associated asthma.[20] According to the GINA 2025 report, high FeNO levels are defined as >50 ppb in ICS-naïve patients, ≥25 ppb in patients treated with medium-dose ICS, and ≥20 ppb in those receiving high-dose ICS therapy.[1] In patients presenting with typical asthma symptoms, elevated FeNO levels may support a diagnosis of type 2 asthma; however, lower values do not exclude asthma.[1]

Serum total IgE

IgE synthesis is driven by interactions between Th2 lymphocytes and B cells, culminating in the stimulation of mast cells and basophils. Serum IgE levels do not consistently reflect asthma severity or treatment response. In addition to asthma, elevated total IgE levels may be observed in conditions such as allergic rhinitis, nasal polyposis, atopic dermatitis, parasitic infections, immunodeficiency syndromes, and allergic bronchopulmonary aspergillosis. Increased IgE levels may occasionally be associated with malignancies, smoking, or high environmental allergen exposure. Anti-IgE therapy may be considered in appropriately selected patients with asthma.[21]

Neutrophils

High levels of airway neutrophils are frequently observed in severe T2-low asthma phenotypes associated with activation of Th17 pathways. Although sputum examination may demonstrate marked neutrophilic inflammation, studies have reported inconsistent correlations between airway and peripheral blood neutrophil counts, highlighting the need for additional diagnostic assessments.[22]

Biologics in Severe Asthma

Severe asthma accounts for less than 10% of all asthma cases but contributes disproportionately to overall morbidity and healthcare costs.[8] Currently, four main classes of biologic agents are approved for the management of severe asthma, targeting IgE, IL-5, IL-4R, and TSLP (Table 1). These biologic therapies have been associated with substantial reductions in exacerbations, healthcare resource utilization (HCRU), and maintenance OCS requirements, along with improvements in patients' quality of life.[12]

Omalizumab

Omalizumab specifically targets the Fc region of IgE. By forming omalizumab–IgE complexes, it effectively reduces circulating free IgE levels.[23]

Omalizumab was approved by the United States (U.S.) Food and Drug Administration (FDA) in 2003 and was the first biologic agent developed for the targeted treatment of moderate-to-severe persistent asthma in adults and adolescents (≥12 years) who are sensitized to perennial aeroallergens and continue to have uncontrolled symptoms despite ICS therapy.[24] Approval by the European Medicines Agency (EMA) followed in 2005, extending its indication as add-on therapy for adolescents and adults (≥12 years) with severe allergic asthma that remains insufficiently controlled despite high-dose ICS plus a long-acting β2-agonist.[25] The approved use

Table 1: Biologic therapies for severe asthma in children and adults

Biologic agent	Target	Indication	Biomarkers	Route of administration	Approved age		Biological effects
					FDA	EMA	
Omalizumab	IgE	Severe allergic asthma	IgE 30–1500 IU/mL[25]	Subcutaneous	≥6 years	≥6 years	Decreases circulating total IgE; Downregulates FcεRI receptors on basophils, mast cells, and dendritic cells
Mepolizumab	IL-5	Severe eosinophilic asthma	Eos ≥150 cells/μL before first administration or Eos ≥300 cells/μL in the previous year[38,44]	Subcutaneous	≥6 years	≥6 years	Blockade of IL-5/IL-5 binding
Benralizumab	IL-5Rα	Severe eosinophilic asthma	Eos ≥300 cells/μL[55]	Subcutaneous	≥6 years	≥18 years	Blockade of IL-5/IL-5R binding
Reslizumab	IL-5	Severe eosinophilic asthma	Eos ≥400 cells/μL[67]	Intravenous	≥18 years	≥18 years	Binds circulating IL-5 to prevent receptor engagement
Dupilumab	IL-4Rα	Severe eosinophilic asthma	Eos ≥150 cells/μL or FeNO ≥25 ppb[78]	Subcutaneous	≥6 years	≥6 years	Blockade of IL-4/IL-4Rα binding; Blockade of IL-13/IL-4Rα binding
Tezepelumab	TSLP	Severe asthma	T2-independent[83]	Subcutaneous	≥12 years	≥12 years	Blockade of TSLP/TSLPR binding

FDA: Food and drug administration, EMA: European medicines agency, Eos: Eosinophils, FeNO: Fractional exhaled nitric oxide, IgE: Immunoglobulin E, IL: Interleukin, IL-4Rα: Interleukin-4 receptor alpha, IL-5Rα: Interleukin-5 receptor alpha, TSLP: Thymic stromal lymphopoietin, T2: Type 2 inflammation, TSLPR: Thymic stromal lymphopoietin receptor.

was subsequently expanded to include patients aged ≥6 years, with pediatric approval granted by the EMA in 2009 and by the FDA in 2016.[24,25]

Omalizumab is administered via the subcutaneous (SC) route at two- or four-week intervals. Dosing is adjusted according to patient weight and baseline total IgE levels, with authorized ranges of 30–1500 IU/mL across the European Union (EU) and 30–700 IU/mL in the U.S. Routine measurement of IgE levels during omalizumab therapy is unnecessary. Reassessment of clinical benefit is recommended after completion of an initial treatment period of approximately four to six months.[24]

Omalizumab is also approved and used in clinical practice for the management of CRSwNP, IgE-mediated food allergies, and chronic spontaneous urticaria.[24,25]

Randomized controlled trials (RCTs) have demonstrated that omalizumab treatment reduces the asthma exacerbation rate (AER) by 25–61%, improves disease-related quality of life, and decreases HCRU by 44%, while also allowing for a reduction in ICS doses.[23,26–28] Pediatric RCTs have shown approximately a 40% reduction in asthma exacerbation rates among children receiving omalizumab compared with those receiving placebo.[29,30] A large Cochrane review published in 2014, which included 25 RCTs involving both adults and children, demonstrated that omalizumab significantly reduced exacerbation frequency (by nearly 25%), lowered hospital admission rates, and facilitated reductions in inhaled ICS requirements.[31] Real-world data have consistently shown that omalizumab treatment is associated with fewer asthma exacerbations and reduced hospital attendance.[32] An integrated analysis combining data from clinical trials and seven years of real-world experience showed that omalizumab therapy in children with moderate-to-severe allergic asthma resulted in improved symptom control, reduced exacerbation rates, fewer hospital visits, and sustained reductions in inhaled corticosteroid use.[33]

Post-marketing surveillance has estimated the risk of anaphylaxis associated with omalizumab at approximately 0.2%, prompting the U.S. FDA to issue a boxed warning.[24]

The EXPECT study (The EXPOSURE in Pregnancy to Omalizumab), a prospective pregnancy registry including 250 women with asthma receiving omalizumab, demonstrated no increased incidence of major congen-

ital anomalies compared to matched controls.[34] Data derived from registries and post-marketing experience further support the absence of an increased risk of congenital anomalies, miscarriage, or preterm delivery.[12]

Mepolizumab

Mepolizumab inhibits the interaction between IL-5 and its receptor (IL-5Rα) on eosinophils, thereby suppressing eosinophil maturation in the bone marrow, reducing extracellular matrix deposition within the airway mucosa, and ultimately attenuating key pathophysiological mechanisms underlying eosinophilic asthma.[16]

Mepolizumab was approved in 2015 by both the U.S. FDA[35] and EMA[36] for the treatment of severe eosinophilic asthma (SEA) in individuals aged ≥12 years. The indication was subsequently expanded to include pediatric patients aged 6–11 years, with EMA approval granted in 2018 and FDA approval following in 2019.[35,36] Mepolizumab is indicated for patients with SEA who have experienced a specified number of asthma exacerbations in the previous year and have BEC above a locally defined threshold (e.g., ≥150 or ≥300/μL), with different cutoffs sometimes applied for patients receiving OCS.[1] The drug is administered via the SC route every four weeks, with a recommended dose of 40 mg for children aged 6–11 years and 100 mg for patients aged ≥12 years.[35,36] Mepolizumab is also approved for the treatment of CRSwNP, hypereosinophilic syndrome, and EGPA.

A multicenter, double-blind, placebo-controlled trial (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma [DREAM]) evaluated three dosing regimens of mepolizumab and demonstrated a 39–52% reduction in the annual AER compared with placebo, along with a prolonged time to first exacerbation.[37] In the MENSA trial (MEpolizumab as adjunctive therapy iN patients with Severe Asthma), which evaluated both SC and intravenous (IV) mepolizumab versus placebo in adolescents and adults, treatment with mepolizumab resulted in a marked reduction in AERs across both routes of administration. In addition, increases in forced expiratory volume in 1 second (FEV_1) occurred rapidly after the first dose and were maintained over time.[38]

In an open-label, non-randomized study involving a small cohort of children aged 6–11 years, designed to assess mepolizumab bioavailability and optimal dosing, no safety signals were identified. Following treatment initiation, blood eosinophil levels declined in association with clinical improvement, whereas lung function parameters showed no significant change.[39] In the MUPPITS-2 trial (MEPolizumab adjUnct therapy in children and adolescents with severe eosInophilic aSthma), which enrolled participants aged 6–17 years, mepolizumab therapy resulted in an approximate 27% reduction in annual AERs compared to the placebo group.[40] However, this improvement was not accompanied by significant enhancements in pulmonary function or other clinical outcomes. The smaller reduction in exacerbation frequency compared to adult studies may reflect differences in the underlying pathophysiology of pediatric asthma.[41]

The COSMEX study (Long-term Safety and Efficacy of Mepolizumab in Patients with Severe Eosinophilic Asthma), which evaluated the long-term effects of mepolizumab, demonstrated that patients receiving mepolizumab experienced sustained reductions in AER and maintenance OCS use, along with improvements in FEV_1 and Asthma Control Questionnaire-5 scores.[42] Additionally, in this study, patients who discontinued mepolizumab for more than 12 weeks experienced a temporary deterioration in symptoms and FEV_1, which resolved rapidly after treatment reinitiation.[42] In the MUSCA study (Mepolizumab in Subjects with Severe Eosinophilic Asthma), mepolizumab produced an early and sustained improvement in FEV_1 compared with placebo and enhanced health-related quality of life (HRQOL) in patients with SEA.[43] In another study involving patients requiring daily OCS therapy, mepolizumab also conferred important clinical benefits, including reduced exacerbation rates, improved symptom control, and a substantial glucocorticoid-sparing effect.[44]

Real-world studies confirm the efficacy and safety profile of mepolizumab observed in clinical trials, particularly with respect to reductions in exacerbation rates, decreased systemic steroid use, improvements in FEV_1, and maintenance of favorable safety profile.[45,46]

A more favorable therapeutic response to mepolizumab has been associated with several clinical characteristics, including higher sputum eosinophil counts, the presence of comorbid CRSwNP, a history of frequent exacerbations at baseline, late-onset disease, lower body mass index, and the use of low-dose maintenance OCS.[47,48]

The most frequently reported adverse events associated with mepolizumab include respiratory tract infections,

headache, bronchitis, and worsening asthma symptoms. An increased incidence of herpes zoster has been observed in patients receiving mepolizumab compared with those receiving placebo.[49] Consequently, the U.S. FDA[35] recommends consideration of herpes zoster vaccination when clinically appropriate. The risk of parasitic infections associated with biologic agents targeting IL-5 and eosinophils remains uncertain. Nevertheless, a parasitic infection occurring during mepolizumab therapy has been reported previously in our clinic.[50]

Data on mepolizumab use during pregnancy are limited and are derived primarily from observational reports rather than interventional clinical studies. In this context, our clinical experience includes a patient who became pregnant while receiving mepolizumab; treatment was discontinued early in gestation, and the pregnancy resulted in a healthy term delivery.[51]

Benralizumab

Benralizumab targets IL-5Rα on eosinophils and basophils, leading to rapid and near-complete eosinophil depletion via antibody-dependent cell-mediated cytotoxicity. Benralizumab was approved in 2017 by the U.S. FDA for use in adults and adolescents (≥12 years) with SEA, and the indication was extended in 2024 to include children aged 6–11 years.[52] It was also approved in 2018 by the EMA for use in adults only, and the pediatric extension is currently under regulatory review.[53]

In pediatric patients aged 6–11 years weighing <35 kg, benralizumab is administered subcutaneously at a dose of 10 mg every four weeks for the first three doses, followed by maintenance dosing at eight-week intervals. In patients weighing ≥35 kg, as well as in adolescents and adults, benralizumab is administered subcutaneously at 30 mg every four weeks for the initial three doses, followed by maintenance treatment every eight weeks.[52]

Benralizumab is an option for patients with uncontrolled SEA and a BEC ≥300 cells/μL. In the SIROCCO study (Study of IL-5 Receptor α mAb in Patients with Severe Asthma) involving adolescents and adults, benralizumab improved pulmonary function, reduced AERs, and decreased OCS dependence in patients with moderate-to-severe asthma.[54] In the double-blind SIROCCO and CALIMA (Cytokine Antibody-mediated Inhibition of IL-5 in Patients with Moderate-to-Severe Asthma) trials, which enrolled adolescents and adults, comparison between benralizumab and placebo demonstrated a 17–40% reduction in exacerbation rates in patients with BECs below 300 cells/μL and a 28–51% reduction in those with BECs ≥300 cells/μL.[54,55] The ZONDA study (Zonal OCS Dose Reduction with Benralizumab in Severe Asthma), which included patients requiring maintenance OCS therapy, demonstrated that benralizumab enabled a 50% reduction in OCS dosage compared with placebo.[56]

Long-term evaluations extending up to five years demonstrated that benralizumab maintained favorable safety and tolerability profiles.[57] Long-term extension data also showed that the clinical benefits of benralizumab were maintained for nearly two years. During this period, approximately 50% of patients experienced no exacerbations, and the AER remained low at 0.56 events per patient-year in patients receiving benralizumab every eight weeks with baseline BEC ≥300 cells/μL. Improvements in lung function persisted, with mean increases in FEV_1 of 0.343 L and 0.364 L after one and two years of treatment, respectively, and gains in HRQOL were maintained.[58] Positive effects on HRQOL were also observed in the ANDHI study (Andalusia Severe Asthma Study with Benralizumab),[59] and real-world evidence further supports the efficacy and safety of benralizumab.[60,61]

Factors associated with enhanced clinical response to benralizumab include adult-onset asthma, a history of more than three exacerbations in the previous year, the presence of nasal polyps, higher baseline BEC, maintenance OCS use, and a pre-bronchodilator forced vital capacity (FVC) below 65% of the predicted value.[54,62]

In the TATE study (Trial of Benralizumab Pharmacokinetics, Pharmacodynamics, and Safety in Pediatric Patients with Severe Asthma), benralizumab demonstrated predictable pharmacokinetics in children aged 6–11 years, which were comparable to those observed in adolescents and adults. Treatment resulted in near-complete depletion of blood eosinophils. Exploratory analyses indicated numerical improvements in pulmonary function (FEV_1) and asthma symptom control, with the annualized exacerbation rate reduced by approximately 50% compared to baseline.[63] Adverse events were reported in 78.6% of participants; most were mild and consisted primarily of nasopharyngitis and local injection-site reactions. None of the adverse events led to treatment discontinuation or death.[63]

Reslizumab

Reslizumab is a monoclonal antibody targeting IL-5, resulting in reduced eosinophil levels in both the bloodstream and the airways. The U.S. FDA[64] and the EMA[65] approved IV reslizumab in 2016 for the treatment of SEA, administered at a weight-based dose of 3.0 mg/kg every four weeks. Reslizumab is indicated for adults (≥18 years) with a history of asthma exacerbations within the preceding year and baseline BECs of at least 400 cells/μL.[66] While some studies have demonstrated significant improvements in FEV_1 and asthma-related symptoms with reslizumab compared to placebo, others have failed to show a meaningful difference between reslizumab and placebo.[67,68] A recent real-world study demonstrated that reslizumab was effective in reducing exacerbation frequency and improving FEV_1 six months after treatment initiation.[69] Further studies are needed to elucidate the role of reslizumab in the mechanisms underlying airway remodeling in patients with asthma.

Dupilumab

Dupilumab inhibits both IL-4 and IL-13 signaling by binding to the IL-4 receptor α chain, which is a shared component of the receptor complexes for these cytokines. IL-4 promotes B-cell differentiation toward IgE production, whereas IL-13 contributes to airway smooth muscle contraction and upregulates enzymes involved in nitric oxide generation in bronchial epithelial cells, resulting in elevated FeNO levels.[70] Dupilumab received FDA[71] approval in 2018 for the treatment of SEA or OCS–dependent asthma in adolescents (≥12 years) and adults, followed by authorization from the EMA[72] in 2019 for the same population. Approval was later extended to include pediatric patients aged 6–11 years, with FDA approval granted in 2021 and EMA approval in 2022.[71,72] In addition to asthma, dupilumab is approved for the treatment of atopic dermatitis, CRSwNP, prurigo nodularis, and eosinophilic esophagitis.[71]

For pediatric patients aged 6–11 years, dupilumab is administered via SC injection at a dose of 100 mg every other week or 300 mg every four weeks for those weighing 15–30 kg, and 200 mg every other week for those weighing ≥30 kg. In this age group, for patients with concomitant moderate-to-severe atopic dermatitis, the dosing regimen includes an initial loading dose of 600 mg followed by 300 mg every four weeks for children weighing 15–30 kg, and an initial loading dose of 400 mg followed by 200 mg every other week for those weighing 30–60 kg.[71] In adolescents (≥12 years) and adults, dupilumab is administered via SC injection, starting with an initial loading dose of 400–600 mg, followed by a maintenance dose of 200–300 mg every two weeks. For patients with OCS–dependent asthma, comorbid moderate-to-severe atopic dermatitis, or adults with concomitant CRSwNP, the higher dose is recommended.[71]

In several RCTs, dupilumab was associated with lower annualized AERs, improved lung function and asthma control, and a favorable safety profile in patients with moderate-to-severe uncontrolled asthma.[70,73] Additionally, in adolescents (≥12 years) and adults with OCS-dependent severe asthma, dupilumab further reduced OCS requirements while lowering the rate of severe exacerbations and improving FEV_1.[74] A large real-world retrospective study, US ADVANTAGE (United States Assessment of Dupilumab Effectiveness in Asthma in a Real-World Setting) involving individuals aged ≥12 years with moderate-to-severe asthma, elevated baseline BEC, and common atopic comorbidities (allergic rhinitis, CRSwNP, and atopic dermatitis) demonstrated that dupilumab effectively reduced AER regardless of baseline exacerbation rate or BEC.[75]

The LIBERTY ASTHMA QUEST trial (Evaluation of Dupilumab in Patients with Uncontrolled, Moderate-to-Severe Asthma) demonstrated that dupilumab treatment improved pulmonary function and reduced markers of T2 inflammation in adolescents with inadequately controlled moderate-to-severe asthma.[76] In the VOYAGE trial (Efficacy and Safety of Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma), which enrolled children aged 6–11 years with poorly controlled moderate-to-severe asthma, add-on dupilumab therapy was associated with reductions in AERs and improvements in lung function and symptom control compared to placebo.[77] In the TRAVERSE (Long-Term Safety and Efficacy of Dupilumab in Patients with Asthma) open-label extension studies, long-term dupilumab therapy maintained a favorable safety profile.[78]

Dupilumab shows greater effectiveness in T2-high asthma, with factors associated with a favorable therapeutic response including a baseline BEC ≥300 cells/μL, elevated FeNO (≥50 ppb), and higher IgE levels (>167 IU/mL). These characteristics are also associated with more pronounced reductions in severe exacerbation rates and improved lung function and overall asthma control.

Table 2: Selection of biologic therapy in severe asthma[87]

Biomarker type	Biomarker value	Preferred biologic options
1. Blood eosinophils	≥1500 cells/μL (eosinophilic asthma)	• Anti–IL-5 • Anti–IL-5R
	≥300–1500 cells/μL (eosinophilic asthma)	• If allergic: Anti-IgE, Anti–IL-4Rα, Anti–IL-5, Anti–IL-5R, Anti-TSLP • If non-allergic: Anti–IL-4Rα, Anti–IL-5, Anti–IL-5R, Anti-TSLP
	≥150–299 cells/μL (eosinophilic asthma)	• If allergic: Anti-IgE, Anti–IL-4Rα, Anti-TSLP • If non-allergic: Anti–IL-4Rα, Anti-TSLP
	<150 cells/μL (non-eosinophilic asthma)	Proceed to FeNO evaluation
2. FeNO	≥25 ppb	• If allergic: Anti-IgE, Anti IL-4Rα, Anti-TSLP • If non-allergic: Anti IL-4Rα, Anti-TSLP
	<25 ppb	• If allergic: Anti-IgE, Anti-TSLP • If non-allergic: Anti-TSLP
3. Allergic sensitization (IgE-mediated)	Present	Omalizumab may be considered across phenotypes (if eligibility criteria are met)
4. Other considerations	Comorbidities (nasal polyposis, atopic dermatitis, ABPA, urticaria)	Selected biologics may provide additional benefit depending on comorbidity profile

Anti-IgE (omalizumab), anti–IL-4Rα (dupilumab), anti–IL-5 (mepolizumab, reslizumab), anti–IL-5R (benralizumab), and anti-TSLP (tezepelumab).
ABPA: Allergic bronchopulmonary aspergillosis.Biomarkers are not the sole determinants of biologic therapy selection and may be concurrently elevated in individual patients. Therefore, treatment decisions should be individualized based on clinical characteristics and comorbidities.

[79] Dupilumab demonstrates a favorable tolerability profile, with adverse events generally mild in nature, most commonly including localized injection-site reactions and transient elevations in eosinophil counts.[70]

Tezepelumab

Tezepelumab is a monoclonal antibody directed against TSLP. Approval was granted by the U.S. FDA[80] in 2021, followed by authorization from the EMA[81] in 2022, for use in adolescents (≥12 years) and adults with severe asthma, irrespective of T2 inflammatory status. Tezepelumab is administered as a 210 mg SC injection every four weeks.[80]

In pivotal clinical trials, tezepelumab significantly reduced asthma exacerbations by 56% compared to placebo in patients with severe asthma, independent of baseline BECs, and improved lung function (mean increase in FEV_1 of 130 mL), asthma control, and HRQOL over a 52-week treatment period.[82,83] Extension studies of tezepelumab in adolescents (≥12 years) and adults demonstrated sustained, clinically meaningful reductions in annualized AERs, with continued treatment providing persistent benefits compared to treatment discontinuation after two years.[84,85] In the SOURCE study (Steroid Reduction with Tezepelumab in Patients with Severe Asthma), which evaluated the effectiveness of tezepelumab in patients with OCS-dependent severe asthma, no significant reduction in OCS dose was observed compared to placebo; however, a beneficial effect was noted in participants with baseline BEC ≥150 cells/μL.[86]

Tezepelumab has demonstrated efficacy in both T2-high and T2-low asthma, with greater benefits observed in patients with higher baseline BEC and FeNO levels. The drug was generally well tolerated, with safety analyses indicating that adverse events were mostly mild in nature, most commonly nasopharyngitis and headache.[83]

Selection of Biologic Therapy

Direct comparative randomized controlled trials evaluating these biologic agents in severe asthma have not been conducted. Eligibility for biologic therapy varies across regions and countries and is influenced by regulatory approvals, local reimbursement policies, and treatment affordability. Criteria guiding the selection of patients for biologic therapy include age, the number of exacerbations in the preceding year, the need for maintenance OCS therapy, lung function parameters, and biomarker profiles such as BEC, FeNO, total serum IgE, and allergen-specific IgE (Table 2).[87] Comorbid conditions, including urticaria, nasal polyposis, and atopic dermatitis, should also be taken into consideration. Patient preference must always be respected, and individuals should be fully informed about dosing frequency and the route of administration.

Phenotypic characterization of exacerbations occurring during biologic therapy may be instrumental in optimizing treatment strategies and guiding decisions regarding switching between biologic agents. According to available data comparing mepolizumab and omalizumab, most exacerbations in both treatment groups are classi-

fied as eosinophilic. This observation raises the possibility that biologic agents providing more effective control of eosinophilia during treatment may offer additional benefit for this patient population.[88]

Remission in Severe Asthma

Biologic therapies effectively target airway inflammation and may induce short- to mid-term remission; however, their ability to confer sustained, long-term disease modification remains uncertain. Clinical remission is defined by symptom resolution, stable pulmonary function, and the absence of OCS use for at least 12 months, whereas complete remission additionally requires suppression of airway inflammation and, when applicable, normalization of bronchial hyperresponsiveness. Several factors have been investigated as potential predictors of remission in patients receiving biologic therapies for severe asthma, including baseline lung function, eosinophil counts, FeNO levels, disease duration, and comorbidities such as nasal polyposis. In our study examining predictors of remission in severe asthma treated with biologic therapy, baseline FEV_1% predicted emerged as an independent determinant of clinical remission in patients receiving mepolizumab or omalizumab. These findings underscore the importance of baseline lung function and suggest a greater potential for remission when biologic therapy is initiated before irreversible airflow limitation develops.[89]

Beyond its physiological burden, severe asthma can impose substantial emotional distress. Evidence indicates that loneliness tends to be more pronounced among patients with poor asthma control and those requiring long-term systemic corticosteroid therapy. Conversely, lower loneliness scores reported in individuals receiving biologic treatments indicate that these agents may confer psychosocial benefits in addition to their established clinical efficacy.[90] In the context of asthma remission, the psychological burden of disease warrants consideration in future research.

Asthma and Biologic Therapies during the COVID-19 Pandemic

At the onset of the COVID-19 pandemic, patients with chronic respiratory diseases were expected to have higher COVID-19–related morbidity and mortality; however, asthma has not been identified as a major risk factor. These findings suggest that asthma does not increase susceptibility to COVID-19, although key aspects of the underlying pathophysiology remain unclear. Early case reports described a mild disease course in patients with severe asthma receiving biologic therapies, supporting the continuation of these treatments during the pandemic. Subsequent reports, however, have suggested that, contrary to these initial observations, some patients with severe asthma treated with biologic therapies may experience a more severe course of COVID-19 compared with the general population. In this context, our clinical observations in patients with severe asthma receiving omalizumab or mepolizumab demonstrated a higher incidence of COVID-19 compared with previously reported data in the literature. Nevertheless, all patients diagnosed with COVID-19 experienced a mild-to-moderate disease course, achieved complete recovery, and no mortality was observed.[91]

Use of Biologic Therapies for Severe Asthma in Türkiye and Reimbursement Criteria

In Türkiye, as in many other countries, biologic agents are used in the management of severe asthma and are reimbursed by the Social Security Institution (Sosyal Güvenlik Kurumu - SGK) for eligible patients.[92] Currently, three biologics (omalizumab, mepolizumab, and benralizumab) are approved and reimbursed for the treatment of severe asthma.

Omalizumab

Omalizumab (brand name: Xolair®) is indicated for patients who met all of the following criteria:

(a) Patients aged ≥12 years with severe persistent allergic asthma and a body weight between 20 and 150 kg;

(b) Inadequate response to treatment with high-dose corticosteroids in combination with long-acting β_2-agonists and/or leukotriene receptor antagonists;

(c) Sensitization to at least one perennial allergen (e.g., house dust mite, cat or dog dander, cockroach, or mold spores), confirmed by skin testing or specific IgE positivity;

(d) Serum IgE level between 30 and 1500 IU/mL.

Prescription of omalizumab requires a 16-week health committee report approved and signed by at least two specialist physicians in pulmonology, immunology, allergy, or allergy and immunology. If a favorable treatment response is documented at the end of the initial 16-week period, a new health committee report valid for

one year is issued indicating treatment efficacy, and the medication is again prescribed by the same specialists.

Mepolizumab and Benralizumab

Mepolizumab (brand name: Nucala®) and benralizumab (brand name: Fasenra®) are indicated for patients with severe persistent eosinophilic asthma who meet all of the following criteria:

(a) Mepolizumab is indicated for children aged ≥6 years, adolescents, and adults, whereas benralizumab is indicated for adults only.

(b) For mepolizumab, a BEC of ≥300 cells/μL is required, or ≥150 cells/μL in patients receiving long-term maintenance systemic corticosteroid therapy; for benralizumab, a BEC of ≥300 cells/μL is required.

(c) Asthma that has been controlled or uncontrolled while receiving maintenance systemic corticosteroid therapy for at least six months, and/or uncontrolled asthma despite at least one year of treatment with high-dose inhaled corticosteroids (>800 μg/day budesonide or equivalent for patients aged ≥12 years; >400 μg/day budesonide or equivalent for children aged 6–11 years) in combination with a long-acting inhaled β_2-agonist and a third controller medication, with at least two exacerbations per year requiring systemic corticosteroid treatment for a minimum of three days per exacerbation.

Reimbursement is provided when the medication is prescribed by specialists in pulmonology or clinical immunology and allergy, based on a health committee report issued by a tertiary healthcare institution that includes at least one specialist in allergy and immunology.

The initial treatment response must be evaluated at week 16 in a tertiary healthcare institution. If continuation of therapy is deemed appropriate, reimbursement is granted when the medication is prescribed by pulmonology or allergy and immunology specialists, based on a new health committee report that includes at least one specialist in allergy and immunology and documents a favorable treatment response.

Conclusion

Although severe asthma represents only a small proportion of the overall asthma population, it accounts for a disproportionate share of asthma-related morbidity, mortality, and overall healthcare burden. The long-term disease-modifying potential of biologic therapies remains incompletely defined, highlighting ongoing uncertainties regarding optimal treatment duration and appropriate strategies for dose adjustment. Given their substantial cost, the clinical value of these agents is maximized when they are prescribed in accordance with appropriate indications.

Selection of the most appropriate biologic therapy should be guided by an individualized assessment of each patient's clinical characteristics. In this context, biomarkers provide valuable insights into asthma endotypes and support informed treatment selection. Biologic therapy should be continued for at least four months before evaluating treatment response; if the response remains unclear during this period, the assessment period may be extended to 6–12 months. Adherence to maintenance inhaled therapy, smoking status, allergen exposure, and other relevant environmental factors should also be systematically evaluated. Asthma remission is increasingly recognized as an achievable clinical goal; however, failure to attain remission may prompt consideration of transitioning to an alternative biologic therapy.

Finally, it is essential to acknowledge the psychological burden associated with severe asthma. Beyond alleviating physiological disease manifestations, biologic therapies appear to confer meaningful improvements in psychological well-being, thereby extending their benefits beyond traditional clinical outcomes.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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