REVIEW ARTICLE

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# Biologic Therapies for Severe Asthma

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Asthma affects more than 300 million people worldwide. Characterized by variable symptoms of shortness of breath, cough, and chest tightness, asthma is associated with chronic airway inflammation, reversible expiratory airflow limitation, and airway hyperresponsiveness.[1] In difficult-to-treat asthma, poor control can be linked to poor adherence to inhaled glucocorticoids, incorrect inhaler technique, and coexisting conditions, including exposure to allergens and irritants.[2] Asthma that is difficult to treat is considered to be severe when control remains poor despite measures that adequately address each of these three variables (see Section I in the Supplementary Appendix, available with the full text of this article at NEJM.org).[3,4]

Up to 10% of adults and 2.5% of children with asthma have severe asthma, with a reduced quality of life and an increased risk of fixed airflow limitation, exacerbations, health care resource use, hospitalization, and death.[5] Patients with severe asthma have persistent symptoms or frequent exacerbations that require repetitive glucocorticoid bursts, maintenance oral glucocorticoid therapy, or both, despite adequate treatment with high-dose inhaled glucocorticoids, long-acting $\beta_2$-agonists, and long-acting muscarinic antagonists.[1] In these patients, add-on treatment, which may include biologic therapies, is needed to reduce the disease burden.

Severe asthma is a heterogeneous syndrome encompassing several clinical phenotypes that differ according to age at the onset of asthma (onset in childhood vs. onset in adulthood), presence or absence of allergy and other coexisting conditions, severity of airflow limitation, frequency of exacerbations, response to treatment, and prognosis.[6] Severe asthma is also heterogeneous biologically, with distinct patterns of airway inflammation defined by the predominant granulocyte in sputum or bronchial biopsy specimens and often identified by means of blood or exhaled-breath biomarkers. Type 2 high-inflammation (type 2–high) asthma is characterized by eosinophilic airway inflammation (Fig. 1), which is associated with increased blood eosinophil counts or elevations of fractional exhaled nitric oxide (FeNO), whereas type 2 low-inflammation (type 2–low) asthma encompasses neutrophilic asthma and paucigranulocytic asthma; the coexistence of eosinophilic and neutrophilic airway inflammation characterizes mixed granulocytic asthma.[7] Approximately 50% of cases of mild-to-moderate asthma and probably a larger proportion of cases of severe asthma are type 2–high asthma.[8,9] This review outlines recent insights into type 2 inflammation in asthma and the currently available biologic treatments, including their mechanism of action, efficacy, and safety in children and adults with severe asthma (Table 1).

## Type 2 Inflammation in Asthma

Type 2 cytokines include interleukin-5, interleukin-4, and interleukin-13 (Section II in the Supplementary Appendix).[10] Interleukin-5 promotes proliferation, differ-

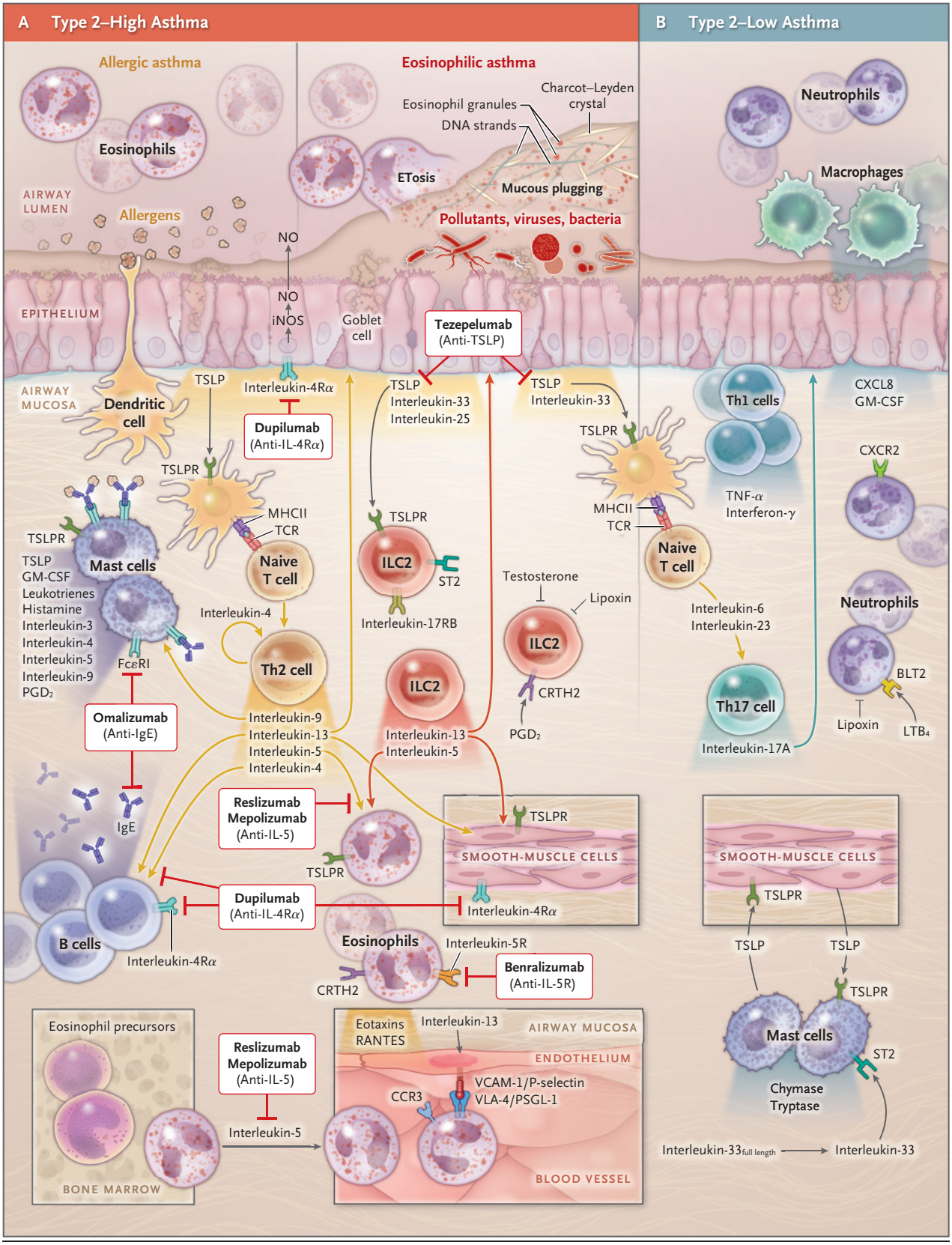

**Figure 1 (facing page). Airway Inflammation in Severe Asthma and Targets of Biologic Therapies.**

The inflammatory pathways of type 2 high-inflammation (type 2–high) asthma (Panel A) or type 2 low-inflammation (type 2–low) asthma (Panel B) drive severe asthma. Type 2–high eosinophilic airway inflammation is present in allergic asthma, most frequently starting in childhood (i.e., childhood-onset asthma), and in adult-onset, severe eosinophilic asthma (which is less often associated with aeroallergy). On exposure to allergens, pollutants, viruses, or bacteria, airway epithelial cells release alarmins (i.e., epithelial cytokines) such as interleukin-25, interleukin-33, and thymic stromal lymphopoietin (TSLP). The pathways involved in type 2–high asthma differ among patients (Panel A). In allergen-sensitized patients, myeloid dendritic cells present inhaled aeroallergens (e.g., house-dust mite, animal dander, or pollen), together with costimulatory molecules, to tissue-resident memory CD4+ type 2 helper T (Th2) lymphocytes, expressing antigen-specific T-cell receptors (TCRs) and responding in an allergen-specific manner on activation. In adult-onset eosinophilic asthma, alarmins released by epithelial cells and eicosanoids (i.e., cysteinyl leukotrienes C4 and D4 and prostaglandin $D_2$ [$PGD_2$]) activate type 2 innate lymphoid cells (ILC2), which lack antigen-specific TCRs but express receptors for these alarmins and leukotrienes. Both Th2 cells and ILC2 produce high amounts of the type 2 cytokines interleukin-4, interleukin-5, and interleukin-13. Interleukin-4 plays a key role in the differentiation of naive CD4+ T cells into Th2 cells and drives IgE isotype switching in B lymphocytes. Interleukin-5 promotes the proliferation and differentiation of eosinophils from bone marrow eosinophil progenitors, prolongs eosinophil survival, and activates eosinophils, which release cysteinyl leukotrienes and toxic granules, causing tissue damage, aggravating chronic airway inflammation, and leading to acute exacerbations of asthma. Interleukin-13 induces expression of the enzyme inducible nitric oxide synthase (iNOS) in epithelial cells, leading to an increase in fractional exhaled nitric oxide (FENO); interleukin-13 also elicits mucous hypersecretion and stimulates contraction of airway smooth-muscle cells, causing bronchoconstriction. Interleukin-4 and interleukin-13 play an important role in recruiting eosinophils from the blood circulation to the airway mucosa both directly, by enhancing the expression of adhesion molecules on endothelial cells, and indirectly, by eliciting the production of chemokines such as eotaxins by epithelial cells. Through eosinophil extracellular traps, Charcot–Leyden crystals, and eosinophil peroxidase–generated oxidants, airway eosinophils mediate mucous plug formation and contribute to chronic airflow obstruction in type 2–high severe asthma. Type 2–low asthma (Panel B) encompasses paucigranulocytic asthma and neutrophilic asthma. Type 1 helper T (Th1) and type 17 helper T (Th17) CD4+ lymphocytes may stimulate neutrophilic inflammation through tumor necrosis factor $\alpha$ (TNF-$\alpha$), interferon-$\gamma$, interleukin-6, interleukin-17A, and CXCL8 (CXC motif chemokine ligand 8). The alarmins TSLP and interleukin-33, the latter activated from full-length interleukin-33 by mast-cell–derived tryptase, may be involved in the cross-talk between mast cells and airway smooth-muscle cells, contributing to airway hyperresponsiveness. ETosis refers to cell death that involves the release of extracellular traps (e.g., by eosinophils or neutrophils). BLT2 denotes leukotriene $B_4$ ($LTB_4$) receptor 2, CCR3 C-C motif chemokine receptor 3, CRTH2 chemoattractant receptor-homologue expressed by Th2 cells, CXCR2 CXC chemokine receptor 2, FcεRI high-affinity receptor for the Fc region of IgE, GM-CSF granulocyte–macrophage colony-stimulating factor, IL interleukin, interleukin-4R$\alpha$ interleukin-4 receptor $\alpha$, interleukin-5R interleukin-5 receptor, interleukin-17RB interleukin-17 receptor B, MHCII major histocompatibility complex class II, PSGL-1 P-selectin glycoprotein ligand 1, RANTES regulated on activation, normal T-cell expressed and secreted, ST2 suppressor of tumorigenicity 2, TSLPR TSLP receptor, VCAM-1 vascular-cell adhesion molecule 1, and VLA-4 very late antigen 4.

entiation, activation, and survival of eosinophils. The numbers of eosinophils in peripheral blood, bronchoalveolar lavage fluid, and bronchial biopsy specimens directly correlate with the severity of asthma.[11] Interleukin-4 and interleukin-13, which share interleukin-4 receptor $\alpha$ (interleukin-4R$\alpha$), have many overlapping functions (Fig. 1). Interleukin-4 plays a key role in CD4+ type 2 helper T lymphocyte differentiation and drives IgE isotype switching in B lymphocytes. Interleukin-13 induces the contraction of airway smooth-muscle cells and stimulates inducible nitric oxide synthase in bronchial epithelial cells, which leads to an increase in FENO (Table S1).

Type 2 inflammation in asthma is generally suppressed by glucocorticoids, as evidenced by a rapid decrease in FENO (mediated by airway interleukin-13) when treatment with inhaled glucocorticoids is initiated and an immediate decrease in blood eosinophil counts (mediated by systemic interleukin-5) with the use of oral glucocorticoids. However, in a subgroup of patients with severe asthma, airway eosinophilia persists despite the use of high-dose inhaled glucocorticoids or oral glucocorticoids.[12]

IgE and type 2 cytokines have been highlighted as therapeutic targets for asthma on the basis of preclinical models of allergic eosinophilic airway inflammation.[10] However, successful translation into treatments for asthma required two crucial insights into the pathogenesis of asthma: an appreciation of the clinical and biologic heterogeneity of the disorder (type 2–high vs. type 2–low asthma)[7] and discovery of the strong association between eosinophilic airway inflammation and the risk of exacerbations.[13] These insights led to the targeting of drugs to patients with eosinophilic asthma and to those with a history of exacerbations.

## ANTI-IGE MONOCLONAL ANTIBODY

The anti-IgE monoclonal antibody omalizumab was the first biologic agent approved by the Food and Drug Administration (FDA) for the treatment of asthma (Table 1). By targeting the Fc fragment of IgE, omalizumab reduces free IgE levels in serum and inhibits binding of IgE to its high-affinity receptor on mast cells and basophils (Fig. 1). In allergen-challenge models in

**Table 1. Biologic Agents Approved by the Food and Drug Administration for the Treatment of Severe Asthma.***

| Biologic Agent (Therapeutic Target and Mechanism of Action) | Route of Administration and Dose† | Forms | Indication | Patient Yr of Age† | Efficacy | Safety Concerns |
|---|---|---|---|---|---|---|
| Benralizumab (interleukin-5Rα; antibody binds to interleukin-5Rα on eosinophils and basophils, depleting them through antibody-dependent, cell-mediated cytotoxicity) | SC; 30 mg every 4 wk (first 3 doses), followed by 30 mg every 8 wk | Prefilled syringe, autoinjector pen | Severe eosinophilic asthma | ≥12 | Reduced exacerbations, reduced symptoms, small or moderate effect on $FEV_1$; decrease or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life | Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs |
| Dupilumab (interleukin-4Rα; antibody binds to interleukin-4Rα, inhibiting interleukin-4 and interleukin-13 signaling in hematopoietic cells [e.g., B cells, CD4+ helper T cells, and eosinophils], epithelial cells, and airway smooth-muscle cells) | Adults and adolescents: SC; initial dose of 400 mg, followed by 200 mg every 2 wk; for glucocorticoid-dependent patients or patients with concomitant moderate-to-severe atopic dermatitis, initial dose of 600 mg, followed by 300 mg every 2 wk<br>Children, ages 6–11 yr: SC; dose depends on body weight‡ | Prefilled syringe, autoinjector pen | Severe eosinophilic asthma (FDA), severe type 2 asthma (EMA), OG-dependent asthma; other indications: CRS with nasal polyposis, moderate-to-severe atopic dermatitis | ≥6 | Reduced exacerbations, reduced symptoms, improved lung function; decrease or withdrawal of OGs, irrespective of blood eosinophil count at baseline; improved quality of life | Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, hypereosinophilic conditions (e.g., EGPA), conjunctivitis |
| Mepolizumab (interleukin-5; antibody binds to circulating interleukin-5) | Adults and adolescents: SC; 100 mg every 4 wk<br>Children, ages 6–11 yr: SC; 40 mg every 4 wk | Prefilled syringe, autoinjector pen | Severe eosinophilic asthma; other indications: EGPA, hypereosinophilic syndrome | ≥6 | Reduced exacerbations, reduced symptoms, small or moderate effect on $FEV_1$; reduction or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life | Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, herpes zoster infections (rare) |
| Omalizumab (IgE; antibody binds to Fc part of free IgE, inhibiting binding of IgE to FcεRI on mast cells and basophils and FcεRII on dendritic cells and eosinophils) | SC; 75 to 375 mg every 2 to 4 wk according to body weight and pretreatment level of serum total IgE | Prefilled syringe | Severe allergic asthma; other indication: chronic idiopathic urticaria | ≥6 | Reduced exacerbations, reduced symptoms, small effect on $FEV_1$; improved quality of life | Serum sickness, hypereosinophilic conditions (e.g., EGPA), abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.2% of patients) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Reslizumab (interleukin-5; antibody binds to circulating interleukin-5) | IV; 3 mg/kg every 4 wk | IV infusion | Severe eosinophilic asthma | ≥18 | Reduced exacerbations, reduced symptoms, small or moderate effect on $FEV_1$; improved quality of life | Helminthic infections, abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.3% of patients) |
| Tezepelumab (TSLP) | SC; 210 mg every 4 wk | Prefilled syringe | Severe asthma | ≥12 | Reduced exacerbations, reduced symptoms, improved lung function; improved quality of life | Pharyngitis, arthralgia, back pain |

* CRS denotes chronic rhinosinusitis, EGPA eosinophilic granulomatosis with polyangiitis, EMA European Medicines Agency, FcεRI high-affinity receptor for the Fc region of IgE, FcεRII low-affinity receptor for the Fc region of IgE, FDA Food and Drug Administration, $FEV_1$ forced expiratory volume in 1 second, interleukin-4Rα interleukin-4 receptor α, interleukin-5Rα interleukin-5 receptor α, IV intravenous, OGs oral glucocorticoids, SC subcutaneous, and TSLP thymic stromal lymphopoietin.

† Information on dose and age is for patients with severe asthma as the main indication.

‡ For pediatric patients, ages 6 to 11 yr, with a body weight of 15 kg to less than 30 kg, the recommended dose of dupilumab is 100 mg every 2 wk or 300 mg every 4 wk; for children with a body weight of 30 kg or more, the dose is 200 mg every 2 wk.

patients with mild allergic asthma, omalizumab limits allergen-induced early- and late-phase asthmatic responses.[14] Omalizumab is approved for subcutaneous administration in persons 6 years of age or older who have moderate-to-severe allergic asthma, with a positive skin-prick test or allergen-specific IgE to a perennial aeroallergen, and whose symptoms are not controlled by inhaled glucocorticoids. A review assessing 25 clinical trials concluded that omalizumab reduced asthma exacerbations and hospitalizations, with small improvements in quality of life and lung function.[15] Anaphylaxis occurs in 0.1 to 0.2% of patients, most frequently with one of the first three doses, and a black-box warning recommends precautions, which include administering the agent in a health care setting and providing patients with adrenaline autoinjectors.

Most studies of omalizumab involved patients with moderate-to-severe asthma who were receiving inhaled glucocorticoids, with only a few studies involving patients with severe asthma. Almost all the studies included patients with allergic asthma (see Glossary) and used threshold levels of serum total IgE as an inclusion criterion. Although the dose of omalizumab (75 to 375 mg administered subcutaneously every 2 to 4 weeks) is based on body weight and the pretreatment serum total IgE level, the absolute level of total IgE does not accurately predict a therapeutic response. In a post hoc analysis, reductions in asthma exacerbations were greater in subgroups of patients with high FENO, blood eosinophil levels, and serum periostin levels than in subgroups with low values.[16] However, identification of biomarkers that accurately predict a therapeutic response to omalizumab is still warranted.[17]

## ANTIBODIES AGAINST INTERLEUKIN-5 AND INTERLEUKIN-5R

Mepolizumab and reslizumab, humanized monoclonal antibodies targeting the ligand interleukin-5, and benralizumab, which depletes eosinophils by binding to the interleukin-5 receptor (interleukin-5R), are FDA-approved biologic agents for the treatment of patients with severe eosinophilic asthma (Table 1). Although initial studies, which enrolled patients who had moderate asthma without evidence of eosinophilic airway

**Glossary**

**Alarmin:** Host protein that is released during infection or tissue damage and that mobilizes and activates immune cells involved in host defense and tissue repair.

**Allergic asthma:** Asthma in patients with aeroallergy, evidenced by a positive skin-prick test or serum allergen-specific IgE (e.g., to house-dust mite, animal dander, or molds) and a clear history of allergen-provoked symptoms.

**Difficult-to-treat asthma:** Asthma with uncontrolled symptoms or frequent exacerbations due to modifiable factors such as incorrect diagnosis; incorrect inhaler technique; poor adherence to inhaled glucocorticoids; exposure to allergens, irritants, or tobacco smoke; and untreated coexisting conditions.

**Endotype:** A disease subtype defined by a distinct pathobiologic mechanism.

**Eosinophilic asthma:** Asthma characterized by eosinophilic airway inflammation, which is associated with increased blood eosinophil counts; in clinical trials and clinical practice, blood eosinophil counts are used as a surrogate marker of airway (or sputum) eosinophilic inflammation.

**Eosinophilic granulomatosis with polyangiitis:** Eosinophilic vasculitis, most frequently antineutrophil cytoplasmic antibody–negative, complicating uncontrolled eosinophilic asthma.

**Innate lymphoid cells:** A novel family of lymphocytes with heterogeneous effector functions and cytokine production; innate lymphoid cells do not express antigen-specific (T- and B-cell) receptors but do express c-kit and receptors for epithelial cytokines. Type 2 innate lymphoid cells are a subtype of innate lymphoid cells that produce type 2 cytokines on activation by epithelial alarmins.

**Periostin:** An interleukin-13–inducible extracellular matrix protein produced by epithelial cells in airways, gut, skin, and other organs.

**Phenotype:** A disease subtype defined by an observable characteristic or trait.

**Severe asthma:** A subset of difficult-to-treat asthma, characterized by asthma that remains uncontrolled despite treatment with high-dose inhaled glucocorticoids combined with a long-acting beta-agonist or leukotriene modifier or treatment with systemic glucocorticoids.

**Type 2 asthma:** Asthma characterized by type 2 airway inflammation, which is associated with increased blood eosinophil counts, elevated fractional exhaled nitric oxide values, or both.

**Type 2 cytokines:** Interleukin-4, interleukin-5, and interleukin-13 cytokines, mainly produced by CD4+ type 2 helper T lymphocytes, type 2 innate lymphoid cells, and mast cells.

**Type 2 inflammation:** Inflammation mediated by one or more type 2 cytokines — interleukin-4, interleukin-5, or interleukin-13 — and characterized by increased IgE levels, eosinophil counts, or fractional exhaled nitric oxide values, respectively.

**Uncontrolled asthma:** Asthma characterized by exacerbations, poor symptom control, lung-function impairment, or a combination of these features.

inflammation, failed to show a benefit of anti–interleukin-5 antibodies, subsequent investigator-initiated trials showed significant reductions in exacerbations among patients with severe eosinophilic asthma.[12,18] In phase 3 studies, add-on treatment with mepolizumab (administered subcutaneously or intravenously) or reslizumab (administered intravenously) reduced exacerbation rates by approximately 50% and improved health-related quality of life in patients with exacerbation-prone severe eosinophilic asthma (i.e., patients with severe eosinophilic asthma who have recurrent exacerbations), irrespective of the presence or absence of allergy.[19-21] Although different cutoff values for blood eosinophil counts were used in these studies, blood eosinophilia was a better predictor of a therapeutic response to anti–interleukin-5 antibody than sputum eosinophil counts or FENO[22,23] (Table S2).

In real-world observational studies, adolescents and adults with severe eosinophilic asthma who were treated with mepolizumab (100 mg administered subcutaneously every 4 weeks) had fewer exacerbations and hospitalizations, a lower oral glucocorticoid burden, and better symptom control and quality of life than in the previous year.[24] In adults with uncontrolled severe eosinophilic asthma, treatment with reslizumab (3 mg per kilogram of body weight, administered intravenously every 4 weeks) was associated with fewer exacerbations, both in randomized, controlled trials (RCTs) and in real-world studies.[20,25] The most frequently reported adverse events in long-term safety studies of mepolizumab and

reslizumab were respiratory infections, headache, and worsening asthma.[26,27] Among 1028 patients receiving intravenous reslizumab, three cases of anaphylaxis were observed, leading to an FDA black-box warning.[27]

Benralizumab is a humanized, afucosylated monoclonal antibody that targets the alpha subunit of interleukin-5R on eosinophils, inducing apoptosis through antibody-dependent, cell-mediated cytotoxicity. In a bronchoscopic study, benralizumab reduced eosinophil counts in the airway mucosa and sputum by 90% or more and completely suppressed blood eosinophil numbers.[28] In two pivotal phase 3 trials involving adolescents and adults with exacerbation-prone severe asthma, add-on treatment with benralizumab (30 mg administered subcutaneously every 4 or 8 weeks) significantly reduced the exacerbation rate and improved prebronchodilator forced expiratory volume in 1 second ($FEV_1$), as compared with placebo, in patients with baseline blood eosinophil counts of 300 per microliter or higher (Table S3).[29,30] Since the every-8-week benralizumab regimen also rapidly improved asthma symptoms and health-related quality of life,[31] this dosing regimen has been chosen for market authorization. Real-world and open-label extension studies have confirmed the real-life effectiveness and long-term safety of benralizumab in patients with severe eosinophilic asthma.[32,33]

More exacerbations in the previous year and a higher blood eosinophil count at baseline are predominant predictors of an enhanced response to anti–interleukin-5 and anti–interleukin-5R antibodies.[34,35] However, a single blood eosinophil measurement, particularly when low, may be insufficient to establish a diagnosis of severe eosinophilic asthma.[36,37] Studies have shown that patients with adult-onset eosinophilic asthma or concomitant nasal polyposis have a good response to anti–interleukin-5 or anti–interleukin-5R antibodies.[38,39] In contrast, in patients with an eosinophilic phenotype of chronic obstructive pulmonary disease (COPD) and a history of exacerbations, add-on therapy with mepolizumab only modestly reduces exacerbations, as compared with placebo; benralizumab does not reduce exacerbations.[40,41] Therefore, it is important to differentiate severe asthma from COPD (Section X.2 in the Supplementary Appendix).

## Anti–Interleukin-4 Receptor Antibody

Dupilumab, a fully human monoclonal antibody, inhibits the signaling of both interleukin-4 and interleukin-13 by binding to interleukin-4R$\alpha$, which they share. In the pivotal phase 3 trial involving patients with uncontrolled moderate-to-severe asthma, dupilumab significantly reduced severe exacerbations, including those leading to emergency-department visits or hospitalization, as compared with placebo (Table S4).[42] Dupilumab also improved asthma control, as well as prebronchodilator and postbronchodilator $FEV_1$.[43] Reductions in the frequency of exacerbations and improvements in lung function were most pronounced among patients with blood eosinophil counts of 150 per microliter or higher or FENO values of 25 parts per billion (ppb) or higher at baseline[42,44] (Fig. S1). In phase 3 trials, patients with eosinophil counts above 1500 per microliter at baseline were excluded. In a real-life retrospective cohort study involving adults with severe asthma (mainly oral glucocorticoid–dependent), add-on therapy with dupilumab was associated with improved asthma control and lung function, as well as reductions in oral glucocorticoid use and the exacerbation rate.[45]

The most common adverse events with dupilumab are injection-site reactions (occurring in 15% of patients).[42,45] Hypereosinophilia (eosinophil count ≥1500 per microliter) is observed in 4 to 25% of patients; it persists after 6 months in 14% of these patients. Although dupilumab-induced hypereosinophilia is most frequently asymptomatic, rare cases of eosinophilic granulomatosis with polyangiitis have been reported.[46]

Dupilumab is effective and is approved by the FDA for the treatment of atopic dermatitis and chronic rhinosinusitis with nasal polyposis, both of which are driven by type 2 inflammation.[47,48] Thus, dupilumab is a convenient treatment for patients with either of these conditions and severe asthma (Section III in the Supplementary Appendix).

## Anti–Epithelial Cytokine Antibodies

The epithelial cytokines TSLP (thymic stromal lymphopoietin), interleukin-25, and interleukin-33

are released by airway epithelial cells in response to allergens, air pollutants, and viruses, enhancing downstream inflammation (Fig. 1).[49] It has been hypothesized that by interfering upstream in the inflammatory cascade, biologic agents targeting epithelial cytokines, as compared with specific antibodies against type 2 cytokines, might improve asthma outcomes in a broader patient population.[49,50] RCTs have recently shown the efficacy of an anti-TSLP human monoclonal antibody (tezepelumab), an anti–interleukin-33 human monoclonal antibody (itepekimab), and a human monoclonal antibody inhibiting the interleukin-33 receptor (also known as suppressor of tumorigenicity 2 [ST2]) (astegolimab) in patients with severe asthma.[51-53]

In a phase 3 RCT involving adolescents and adults with uncontrolled severe asthma, add-on therapy with the anti-TSLP human monoclonal antibody tezepelumab, at a dose of 210 mg administered subcutaneously every 4 weeks, significantly reduced the annualized asthma exacerbation rate by 56%, and among patients with blood eosinophil counts of less than 300 per microliter at baseline, the rate was reduced by 41%.[51] As compared with placebo, tezepelumab reduced exacerbations in patients with type 2–high asthma and patients with type 2–low asthma (Fig. S2) and also improved lung function, asthma control, and health-related quality of life (Table S5). Tezepelumab rapidly reduced blood eosinophil counts and FENO, gradually decreased serum total IgE levels, and attenuated airway hyperresponsiveness to mannitol.[54,55] The safety findings were similar for active treatment and placebo.[51] In a mechanistic bronchoscopy study, tezepelumab significantly reduced the number of eosinophils — but not the number of neutrophils, mast cells, or T cells — in the airway submucosa.[55]

Itepekimab, at a dose of 300 mg administered subcutaneously every 2 weeks, prevented loss of asthma control and improved lung function, as compared with placebo, in a phase 2 study involving patients who had moderate-to-severe asthma and were reducing their maintenance therapy with inhaled glucocorticoids plus long-acting beta-agonists.[52] The combination of itepekimab and dupilumab did not provide benefits beyond those of the individual treatments. Astegolimab (70 mg or 490 mg, but not 210 mg, administered subcutaneously every 4 weeks) reduced exacerbations, as compared with placebo, in a phase 2b RCT involving patients with severe asthma, including those with low eosinophil counts.[53] Astegolimab did not improve lung function. Confirmatory phase 3 RCTs of antibodies against interleukin-33 and ST2 in patients with severe asthma, particularly type 2–low, are warranted.

## BIOLOGIC THERAPIES AS ORAL GLUCOCORTICOID–SPARING AGENTS

Systemic glucocorticoids are commonly used for the management of severe asthma, as short-term courses or long-term daily oral regimens, but are associated with acute and chronic adverse effects.[56] The burden of oral glucocorticoid–associated disorders increases with the cumulative dose and adds to the burden of severe asthma. Moreover, whereas asthma is not associated with an increased severity of coronavirus disease 2019 (Covid-19),[57] use of oral glucocorticoids for uncontrolled severe asthma has been linked to increased Covid-19–related mortality[58] (Section VI in the Supplementary Appendix).

In clinical trials, several anticytokine antibodies enabled tapering of oral glucocorticoids with the use of predefined schedules while asthma control was maintained in adults with glucocorticoid-dependent severe asthma (Table S6). Mepolizumab (100 mg administered subcutaneously every 4 weeks) reduced the glucocorticoid dose by a median of 50%, as compared with placebo, while reducing the annualized rate of exacerbations by 32% and improving asthma control,[59] findings that were supported by real-life observational studies.[60] Mepolizumab has been approved by the FDA at a higher dose (300 mg administered subcutaneously every 4 weeks) for the treatment of eosinophilic granulomatosis with polyangiitis in patients with uncontrolled asthma.[61]

Benralizumab (30 mg administered subcutaneously every 4 or 8 weeks) significantly reduced the median oral glucocorticoid dose from baseline to 28 weeks, as compared with placebo (a 75% reduction vs. a 25% reduction).[62] The annual exacerbation rate was also reduced, although there was no sustained effect on $FEV_1$. Add-on treatment with dupilumab (300 mg adminis-

tered subcutaneously every 2 weeks) reduced the oral glucocorticoid dose by 70%, as compared with 42% with placebo, while reducing severe exacerbations and improving lung function.[63] Although the magnitude of the glucocorticoid-sparing effect with dupilumab treatment was largest in patients with a higher blood eosinophil count at baseline, dupilumab provided benefits even in the low-eosinophil subgroup.

In contrast, neither fixed-dose subcutaneous reslizumab (110 mg every 4 weeks) nor fixed-dose subcutaneous tezepelumab (210 mg every 4 weeks) reduced the daily oral glucocorticoid dose in patients with glucocorticoid-dependent severe asthma.[64,65] Although subgroup analyses suggest that patients with oral glucocorticoid–dependent severe asthma have better asthma control when receiving omalizumab, a prospective evaluation is required to determine whether omalizumab has glucocorticoid-sparing effects.

## BIOLOGIC AGENTS IN CHILDREN AND ADOLESCENTS WITH SEVERE ASTHMA

The anti-IgE monoclonal antibody omalizumab has been studied extensively in moderate-to-severe pediatric asthma. A meta-analysis of three RCTs involving 1380 children with allergic asthma showed that omalizumab reduced exacerbations and hospitalizations, was associated with a larger reduction of inhaled glucocorticoids, as compared with placebo, and had an acceptable adverse-event profile[66] (see the Supplementary Appendix). Some phase 3 trials of anti–type 2 cytokine antibodies have included adolescents (≥12 years of age) (Table S7). A post hoc meta-analysis involving 34 adolescents with eosinophilic severe asthma who were included in randomized trials suggested similar effects in this group and in the overall population studied, but the small sample precluded conclusions. The safety profile among adolescents appeared to be similar to that among adults, although as noted, the number of patients who could be evaluated was small.[67] A recent open-label, observational study confirmed the safety of mepolizumab in children (6 to 11 years of age) with severe asthma and showed a reduction in exacerbations, as compared with baseline.[68] Since the type 2–high, eosinophilic phenotype is often observed in children with severe asthma and recurrent exacerbations,[69] it seems likely that anti–type 2 cytokine antibodies will be efficacious in children with severe asthma who are prone to exacerbations.[70] In an RCT involving 408 children (6 to 11 years of age) with uncontrolled moderate-to-severe asthma, dupilumab significantly reduced severe asthma exacerbations and improved lung function and asthma-related quality of life, with the most pronounced effects in the population of children with type 2–high asthma and baseline blood eosinophil counts of 150 per microliter or higher or FENO values of 20 ppb or higher.[71] The safety profile was acceptable. In prior analyses of predictors of the response to benralizumab or reslizumab, older age (≥18 years vs. <18 years) and a later onset of eosinophilic asthma (onset in adulthood vs. childhood) were associated with enhanced efficacy.[34,38] These observations underline the need for RCTs that involve well-characterized children with severe asthma and include long-term follow-up for evaluation of safety (Section IV and Table S7 in the Supplementary Appendix).

## CHOOSING INITIAL BIOLOGIC THERAPY

Since no data from head-to-head RCTs comparing the efficacy, real-life effectiveness, and long-term safety of monoclonal antibodies in patients with severe asthma are available, high-level evidence is lacking to guide clinical decision making. Before a biologic therapy is initiated, the number of exacerbations in the past year, status with respect to oral glucocorticoid use, biomarkers (blood eosinophil count, FENO, and serum total and allergen-specific IgE), $FEV_1$, asthma control, and quality of life should be recorded. Criteria such as dosing frequency, route of administration (subcutaneous or intravenous), whether drug administration requires monitoring by health care personnel, age at onset of asthma, biomarkers, coexisting conditions (e.g., atopic dermatitis and nasal polyposis), insurance coverage, cost, and patient preference are taken into account in choosing an available therapy.[35] Biomarkers and coexisting conditions should be integrated with clinical phenotyping in decision making regarding the choice of the initial biologic therapy (Fig. 2 and Table 2).

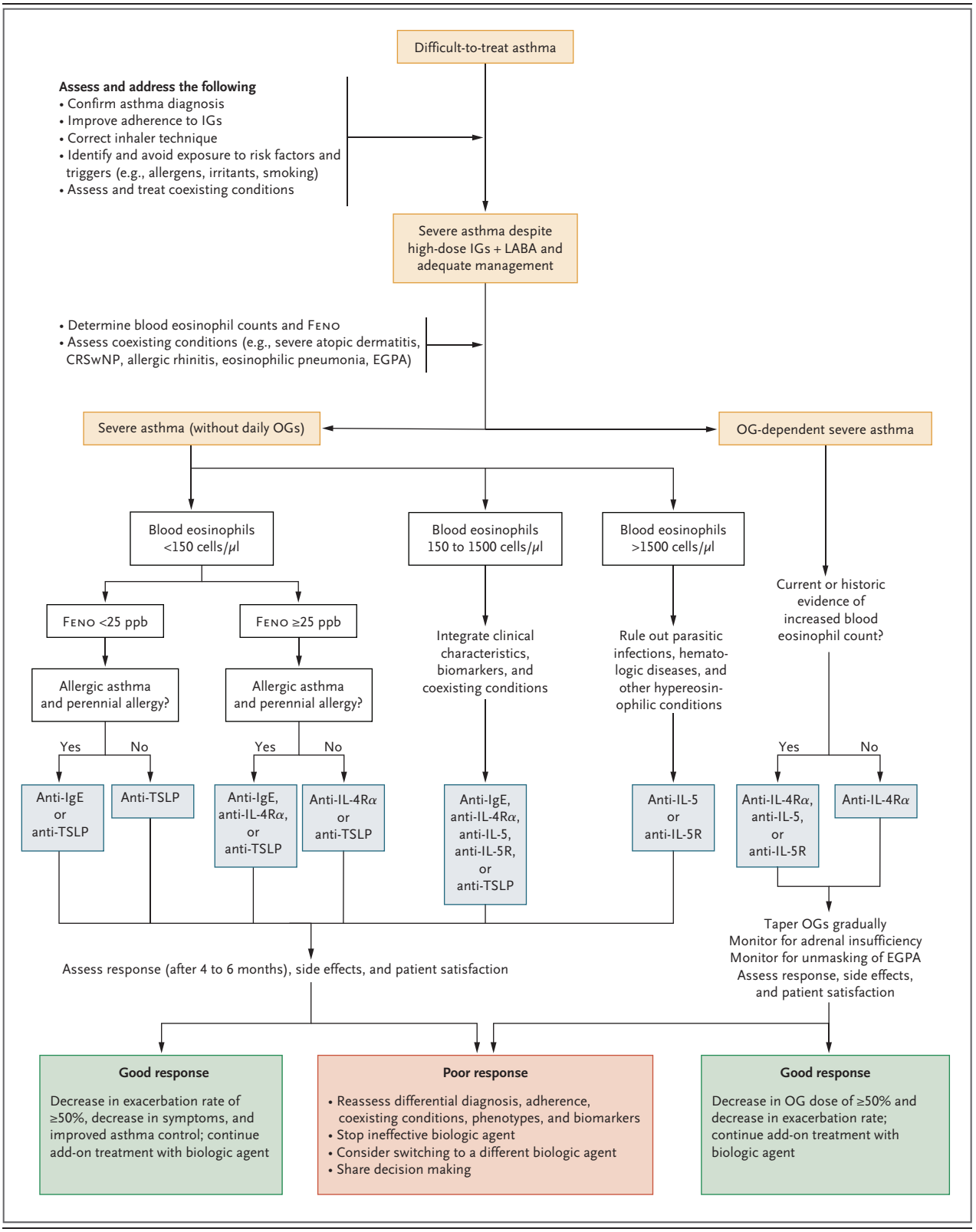

**Figure 2 (facing page). Algorithm for the Assessment and Treatment of Adults with Uncontrolled Severe Asthma.**

The management of uncontrolled severe asthma encompasses multiple steps: first, confirming the diagnosis by differentiating difficult-to-treat asthma from severe asthma; second, determining the phenotype of severe asthma by integrating clinical characteristics, biomarkers, and coexisting conditions in order to choose the appropriate initial biologic therapy[72]; and finally, monitoring the therapeutic response and side effects to decide whether the biologic agent should be continued or stopped (and switched, if feasible). An increasing blood eosinophil count indicates improvement in the treatment response to the biologic agent. The monoclonal antibodies, listed in alphabetical (and numerical) order, are anti-IgE antibody (omalizumab), anti-IL-4R$\alpha$ antibody (dupilumab), anti-IL-5 antibody (mepolizumab or reslizumab), anti-IL-5R antibody (benralizumab), and anti-TSLP antibody (tezepelumab). CRSwNP denotes chronic rhinosinusitis with nasal polyposis, EGPA eosinophilic granulomatosis with polyangiitis, IGs inhaled glucocorticoids, LABA long-acting $\beta_2$-agonist, OGs oral glucocorticoids, and ppb parts per billion.

## MONITORING OF BIOLOGIC THERAPIES

Management should be individualized according to the "assess, adjust, and review response" cycle.[1] A 4-to-6-month treatment period is needed to assess the effectiveness of a biologic agent; safety issues may arise early in that interval (e.g., eosinophil elevations with dupilumab or injection-site reactions with all treatments). Although at present there are no well-defined criteria for a good response to a biologic agent, a reduction in the number of exacerbations and improvement in asthma symptoms and quality of life are key outcomes, which should be defined a priori by doctor and patient together.

In patients with oral glucocorticoid–dependent severe asthma, the percentage reduction in the glucocorticoid dose with maintenance of asthma control is a critical outcome measure.[73] In addition, use of health care services, degree

**Table 2. Choice of Monoclonal Antibody Treatment of Severe Asthma According to Patient Characteristics.***

| Characteristic | Anti-IgE Antibody | Anti–Interleukin-4R Antibody | Anti–Interleukin-5 or Anti–Interleukin-5R Antibody |
|---|---|---|---|
| Indication | Severe allergic asthma | Severe type 2 asthma | Severe eosinophilic asthma |
| Age group | Children, adolescents, and young adults | Children, adolescents, and adults | Adults |
| Onset | Childhood | Childhood or adulthood | Adulthood |
| Allergy | Prerequisite: IgE sensitization to perennial allergen | Irrespective of allergy | Irrespective of allergy |
| Dominant biomarker | Serum total IgE (for dosing) | Increased FENO | Increased blood eosinophil count |
| Serum total IgE | Serum total IgE and weight within dose range, according to local eligibility criteria | Irrespective of total IgE | Irrespective of total IgE |
| Blood eosinophil count† | Slightly better response with increased count | >150 to <1500/$\mu$l† | Prerequisite: increased counts (according to local eligibility criteria), >150 to 300/$\mu$l† |
| FENO† | Slightly better response if increased FENO | Better response if FENO >25 ppb | Irrespective of FENO |
| Coexisting conditions | Allergic rhinitis, CRS with nasal polyposis, chronic urticaria | Atopic dermatitis, CRS with nasal polyposis | CRS with nasal polyposis |
| Exacerbations in previous yr | According to local criteria | According to local criteria | High frequency (≥2), as specified by local criteria |

* In December 2021, the anti-TSLP antibody tezepelumab was approved by the FDA for the add-on maintenance treatment of adults and pediatric patients 12 years of age or older who have severe asthma, with no phenotype (e.g., allergic or eosinophilic) or biomarker limitation within its approved label (Fig. S2 in the Supplementary Appendix). FENO denotes fractional exhaled nitric oxide, and ppb parts per billion.

† Blood eosinophil counts and FENO values are for patients with severe asthma who are not receiving maintenance oral glucocorticoid therapy.

of lung-function improvement, effect on coexisting conditions, side effects, and patient satisfaction need to be taken into account. If a patient has an inadequate response, with persistent symptoms or exacerbations, nonadherence to background controller therapy or the biologic agent itself should be evaluated. Whereas several biologic agents are available as an autoinjector pen, the potential for poor adherence with home dosing should be considered and adherence should be improved before switching to a different biologic agent. Inadequate management of coexisting conditions (e.g., obesity and chronic rhinosinusitis) and the development of neutralizing antidrug antibodies may also underlie suboptimal responses to biologic therapy. Finally, the asthma phenotype, including biomarkers (blood eosinophil count, FENO, and serum IgE level), should be reassessed before switching to another biologic agent (Section XIII in the Supplementary Appendix). Adding a second biologic therapy is currently not recommended because of the incremental costs and the lack of high-quality evidence in support of this approach.

## FUTURE PROSPECTS

For uncontrolled, severe, type 2–high asthma, data are required to better inform the choice of biologic therapy (Table 1).[74] There is an urgent need for biomarkers that accurately predict the therapeutic response (predictive biomarkers) and for early markers of the response to therapy (monitoring biomarkers). Adaptive platform trials are anticipated to facilitate rapid evaluation of new interventions in biomarker-defined subgroups of patients with severe asthma.[75] In addition, pragmatic trial platforms are needed to conduct head-to-head RCTs of different biologic agents to determine their comparative effectiveness in patients with severe asthma.[76,77] The responses to biologic agents in such patients differ, ranging from an excellent response to no response.[33,34,77] Since biologic therapies are expensive, targeted use of these antibodies in patients most likely to benefit from them is warranted.

Several other research questions need to be addressed. First, what is the risk of immunogenicity of the monoclonal antibodies in patients with severe asthma? The development of neutralizing antidrug antibodies might impair the effectiveness of the agent.[33] Therapeutic drug monitoring should be explored in patients with suboptimal responses.[37] Second, how long do patients with severe asthma need to be treated with these biologic agents? There is a need for long-term studies investigating the effect of the agents on the course of the disease, such as a change in the underlying asthma endotype, whether the target of biologic therapy occurs downstream from an inciting event, or perhaps even amelioration of the severity of asthma or remission.[78] Third, more data are needed on the efficacy and safety of biologic therapies in special populations (e.g., children, adolescents, and pregnant women[79,80]; populations whose genetic ancestry was not well represented in the clinical registration trials; and elderly patients). Severe asthma disproportionately affects Black populations, which along with other groups most affected, have been underrepresented in clinical trials.[81,82] Future studies are needed to better enable the assessment of adequate and equitable care for all communities affected by asthma.[83]

Finally, no biologic treatments are currently available for type 2–low severe asthma,[7] which is characterized by neutrophilic or paucigranulocytic airway inflammation and is associated with older age, adult-onset asthma, obesity, metabolic syndrome, hypertension, and greater resistance to treatment with glucocorticoids.[84] Although the pathophysiological features of type 2–low asthma still need to be elucidated, several molecular mechanisms have been implicated, including interleukin-6, CXCL8 (CXC motif chemokine ligand 8), interleukin-17A, interleukin-23, interferon-$\gamma$, tumor necrosis factor $\alpha$, interleukin-33, and TSLP.[85] Recently, the anti-TSLP antibody tezepelumab was shown to reduce exacerbation rates among patients with severe, uncontrolled asthma, irrespective of the blood eosinophil count at baseline,[51] whereas the anti–interleukin-23 monoclonal antibody risankizumab did not provide a clinical benefit in patients with severe asthma.[86]

## CONCLUSIONS

Biologic agents are efficacious add-on therapies for uncontrolled, severe eosinophilic asthma. These therapies represent major breakthroughs,

significantly decreasing exacerbation rates and improving the quality of life and asthma control for patients with type 2–high severe asthma. RCTs involving patients with oral glucocorticoid–dependent severe asthma have shown that add-on therapy with mepolizumab, benralizumab, or dupilumab is glucocorticoid-sparing and reduces exacerbation rates. The ultimate aim is to prevent both short-term and long-term oral glucocorticoid use in people with severe asthma. More recently, tezepelumab, targeting the epithelial alarmin TSLP, has shown efficacy in a broader patient population, including patients with type 2–low severe asthma. Head-to-head trials of monoclonal antibodies against IgE, type 2 cytokines, and alarmins will pave the way toward optimized precision medicine for patients with severe asthma.

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