



REVIEW

Severe Asthma and Biological Therapy: When, Which, and for Whom

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ABSTRACT

Asthma is a heterogeneous chronic inflammatory disease of the airways that affects approximately 300 million people worldwide. About 5–10% of all asthmatics suffer from severe or uncontrolled asthma, associated with increased mortality and hospitalization, reduced quality of life, and increased health care costs. In recent years, new treatments have become available, and different asthma phenotypes characterized by specific biomarkers have been identified.

Biological drugs are currently indicated for patients with severe asthma that is not controlled with recommended treatments. They are mostly directed against inflammatory molecules of the type 2 inflammatory pathway and are effective at reducing exacerbations, maintaining control over asthma symptoms, and reducing systemic steroid use, which is associated with well-known adverse events. Although biological drugs for severe asthma have had a major impact on the management of the disease, there is still a need for head-to-head comparison studies of biologics and to identify new biomarkers for asthma diagnosis, prognosis, and response to treatment. Identifying novel biomarkers could facilitate the development of therapeutic strategies that are precisely tailored to each patient's requirements.

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Key Summary Points

Asthma is a heterogeneous chronic inflammatory airway disease that affects approximately 300 million people worldwide, with about 5–10% of all asthmatics suffering from severe or uncontrolled asthma.

This narrative review analyzes the impact of biological agents that are currently approved and under investigation in order to aid the selection by clinicians of the appropriate biological drug for the management of each severe asthma phenotype.

There is medical need for head-to-head comparison studies of biologics as well as to identify biomarkers for asthma diagnosis, prognosis, and response to treatment.

It is important to identify prognostic and therapeutic biomarkers that characterize specific phenotypes of severe asthma, as this should allow therapeutic strategies that are specifically tailored to individual patients to be devised.

Identifying novel biomarkers could facilitate the development of therapeutic strategies that are precisely tailored to each patient's requirements.

INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease of the airways characterized by chronic airway inflammation, bronchoconstriction, airway hyperresponsiveness, and mucus hypersecretion. Typical symptoms are wheezing, shortness of breath, chest tightness, and cough with variable expiratory flow limitation [1]. Asthma affects approximately 300 million people worldwide, and about 5–10% of all asthmatics suffer from severe or

uncontrolled asthma, which is associated with increased mortality and hospitalization, reduced quality of life (QoL), and increased health care costs. According to the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force, asthma is defined as severe when it “requires treatment with high dose inhaled corticosteroids (ICSs) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy” [1].

Primary endpoints of asthma management are symptom control, fewer exacerbations, improved lung function, and minimization of the long-term adverse events (AEs) of therapies [1]. However, the widely used steps of care approach to asthma treatment is often ineffective due to the heterogeneity of asthma and the extreme variability in the response of asthma to available medications [2]. Furthermore, many patients continue to have poor symptom control and to suffer from recurrent exacerbations despite strictly adhering to therapy [3]. Improvements in our knowledge of the etiopathological mechanisms of different phenotypes and endotypes of severe asthma have led to the availability of innovative therapies in the last few years. For example, biological drugs for severe asthma, most of which are directed against molecules involved in the type 2 inflammatory pathway, modify the natural history of the disease.

The aim of this narrative review is to discuss the effects of biological drugs that are currently approved or under investigation in order to aid clinicians who are attempting to select the appropriate biological agent for managing T helper 2 (Th2)-high/severe asthma phenotypes. This article is based on reviews of current guidelines and literature and does not involve any studies with human participants or animals.

SEVERE ASTHMA PHENOTYPES AND BIOLOGICAL THERAPY

Asthma is a chronic airway disease that is highly heterogeneous in terms of its pathogenesis,

clinical manifestations, severity of symptoms, and outcomes. Recently, the integration of genetics, biology, and clinical features and an improved understanding of asthma pathogenesis have led to the identification of different asthma phenotypes characterized by specific biomarkers. Two major groups of asthma phenotypes that can be distinguished based on the inflammatory pathway involved, namely Th2-high and Th2-low phenotypes, have been recognized. Th2-high-related inflammation is the main characteristic of Th2-high phenotypes, together with early-onset allergic asthma and late-onset eosinophilic asthma. Neutrophilic asthma and obesity-related asthma are considered Th2-low phenotypes [4].

In allergic asthma, the allergens presented to naive CD4⁺ T cells by dendritic cells (DCs) induce differentiation into Th2 cells. In nonallergic eosinophilic asthma, respiratory epithelium-derived cytokines and chemokines such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33 (also called alarmins) are released in response to various harmful triggers (air pollutants, microbes, or glycolipids) [5]. Alarmins bind to the receptors on type-2 innate lymphoid cells (ILC2s). Both of these types of activated cells (Th2 cells and ILC2s) produce cytokines such as IL-4, IL-5, and IL-13, which are the principal effectors of type 2 inflammation [6, 7]. IL-5 is the most specific trigger for eosinophils, as it drives eosinophil maturation in bone marrow, recruitment, and activation [8]. IL-4 and IL-13, which share a common receptor subchain (IL-4R α), induce allergen-specific immunoglobulin (Ig) E synthesis. IgE, through its interaction with the specific receptor Fc ϵ RI (expressed in different immune cells), promotes the release of mediators that are responsible for functional and structural modifications of the bronchial wall. Also, IL-13 activates epithelial inducible nitric oxide (NO) synthase, leading to increased airway NO production, periostin expression in lung epithelial cells and fibroblasts, mucus production by goblet cells, and airway smooth muscle contractility [9].

Approximately 40–50% of all patients with asthma present the early-onset allergic phenotype. These patients develop the disease during

childhood and are characterized by atopy, polysensitization to allergens, high total IgE, high fractional exhaled NO (FeNO) levels, increased sputum and blood eosinophils, and increased airway periostin. High levels of IgE, FeNO, eosinophils, and airway periostin are considered biomarkers of Th2-high-related inflammation. Some of these biomarkers, such as eosinophils and FeNO, are also associated with the late-onset eosinophilic asthma phenotype [4, 10]. Interestingly, eosinophils and FeNO are considered valid non invasive biomarkers of type 2 asthma, as they yield acceptable detection accuracy. However, their levels can be influenced by infections, by exposure to allergens and steroids, and by age, height, sex, and smoking habit [11]. In any case, since sputum eosinophil count of $\geq 3\%$ is well correlated with type 2 asthma, it continues to generate considerable clinical research interest [12]. Approximately 25% of all patients with severe asthma present the late-onset eosinophilic phenotype [13], which is often characterized by a nonsignificant response to treatment with corticosteroids (CSs). This evidence indicates that the Th2 process is separate from the underlying early-onset allergic phenotype, and that blood/sputum eosinophilia can be used as a biomarker to select patients who should be responsive to anti-eosinophilic therapies, including anti-IL-5 [14]. Moreover, adult eosinophilic asthma is sometimes associated with chronic sinusitis and nasal polyps in patients without a clear history of atopy.

Th2-low phenotypes are characterized by a prevalent Th1- and Th17-driven immunity, neutrophilic inflammation, infection, and oxidative stress. These phenotypes are also associated with obesity and systemic inflammation, including increased levels of different cytokines such as tumor necrosis factor alpha (TNF- α), IL-6, and leptin [15]. Biological therapy of Th2-low asthma phenotypes will not be discussed in the present narrative review.

Increased knowledge of molecular pathways and the characterization of severe asthma phenotypes may help to drive the use of novel biological therapies that have been approved or are under investigation. Biological therapy has been demonstrated to be effective at reducing asthma exacerbations, maintaining control over

Table 1 Pivotal studies of biological agents and investigated outcomes

Biological drug	Target	Study identifier	Main outcomes		Lung function	OCS-sparing effect
			Asthma exacerbations			
Omalizumab	IgE	NCT00314575 [20]	25% reduction	NA	NA	NA
		EXTRA study, NCT00314574 [21]	Greater reduction in protocol-defined exacerbations in high vs. low subgroups for all biomarkers: FeNO 53% vs. 16%; eosinophils 32% vs. 9%; periostin 30% vs. 3%	NA	NA	NA
Mepolizumab	IL-5	ICATA STUDY, NCT00377572 [23]	18.5% reduction in annualized exacerbation rate	NA	NA	NA
		XPORT study, NCT00314574, [29]	67% with no exacerbations in omalizumab arm vs. 48% in placebo arm	NA	NA	NA
Mepolizumab	IL-5	DREAM study, NCT01000506 [14]	48% reduction in the 75 mg mepolizumab arm; 39% reduction in the 250 mg mepolizumab arm; 52% reduction in the 750 mg mepolizumab arm	NA	NA	NA
		MENSA study, NCT01691521 [39]	47% reduction in exacerbation rate in the IV mepolizumab arm, 53% reduction in exacerbation rate in the SC mepolizumab arm compared to placebo	Mean increase from baseline in FEV ₁ : 100 ml in the IV mepolizumab arm compared to placebo; mean increase from baseline in FEV ₁ : 98 ml in the SC mepolizumab arm compared to placebo	NA	50% reduction in glucocorticoid dose in the mepolizumab arm vs. 0% reduction in glucocorticoid dose in the placebo arm
Mepolizumab	IL-5	SIRIUS study, NCT01691508 [40]	32% reduction in annualized exacerbation rate	NA	NA	OCS dose reduction achieved with mepolizumab in the SIRIUS study was maintained; patients treated with placebo in the SIRIUS study achieved a reduction in OCS dose from 12.3 mg/day to 5.0 mg/day after 1 year of treatment with mepolizumab
		COSMOS study, NCT01842607 [41]	Annualized rate of 0.93 on-treatment exacerbations	NA	NA	NA
Mepolizumab	IL-5	COLUMBA study, NCT01691859 [42]	61% reduction in annualized rate of on-treatment exacerbations (0.68 events) compared to the off-treatment period between DREAM and COLUMBA studies	NA	NA	NA
		COSMEX study, NCT02135692 [43]	Annualized rate of 0.93 on-treatment exacerbations; annualized rate of 0.13 exacerbations requiring hospitalization or emergency visit; annualized rate of 0.07 exacerbations requiring hospitalization	NA	NA	NA

Table 1 continued

Biological drug	Target	Study identifier	Main outcomes		
			Asthma exacerbations	OCS-sparing effect	
			Lung function		
Reslizumab	IL-5	NCT01508936 [46]	NA	FEV ₁ in subgroup with eosinophils < 400 cells/ μ l: 33 ml greater compared to placebo. FEV ₁ in patients with eosinophils \geq 400/ μ l: 270 ml greater compared to placebo	NA
		NCT01287039, NCT01285323 [47]	Study 1: 34% reduction in frequency of clinical asthma exacerbation events; study 2: 31% reduction in frequency of clinical asthma exacerbation events	Improvement in FEV ₁ in reslizumab arms compared to placebo in both trials	NA
Benralizumab	IL-5R	SIROCCO study, NCT01928771 [53]	Reduction in annual asthma exacerbation rate (up to 51%) over 48 weeks in Q4W and Q8W regimens compared to placebo	Pre-bronchodilator FEV ₁ (up to 159 ml) improvement in Q4W and Q8W regimens compared to placebo	NA
		CALIMA study, NCT01914757 [54]	Lower annual exacerbation rates in the Q4W or Q8W regimens compared to placebo	Pre-bronchodilator FEV ₁ improvement in the Q4W and Q8W regimens	NA
		ZONDA study, NCT02075255 [55]	55% reduction in annual exacerbation rate compared to placebo	NA	75% mean reduction in oral glucocorticoid dose in both benralizumab dosage regimens vs. 25% reduction in placebo arm
		BORA study, NCT02258542 [56]	Patients with eosinophils \geq 300 cells/ μ l: annualized rate of on-treatment exacerbations was 0.50 in Q4W vs. 0.49 in Q8W regimens, annualized rate of exacerbations requiring an emergency visit was 0.03 in Q4W vs. 0.05 in Q8W regimens, annualized rate of exacerbations requiring hospitalization was 0.04 in both Q4W and Q8W regimens. Patients with eosinophils < 300 cells/ μ l: annualized rate of on-treatment exacerbations was 0.76 in Q4W vs. 0.64 in Q8W regimens, annualized rate of exacerbations requiring an emergency visit was 0.03 in Q4W vs. 0.04 in Q8W regimens, annualized rate of exacerbations requiring hospitalization was 0.06 in Q4W vs. 0.05 in Q8W regimens	Change in pre-bronchodilator FEV ₁ from baseline in patients with < 300 eosinophils/ μ l: - 17 ml in Q4W vs. - 1 ml in Q8W regimens; change in pre-bronchodilator FEV ₁ from baseline in patients with \geq 300 eosinophils/ μ l: 38 ml in Q4W vs. 40 ml	NA

Table 1 continued

Biological drug	Target	Study identifier	Main outcomes	Asthma exacerbations	Lung function	OCS-sparing effect
Dupilumab	IL-4R α	NCT01854047 LIBERTY ASTHMA QUEST, NCT02414854 [60]	33.2–70.5% reduction in annualized exacerbation rate Adjusted annualized exacerbation rate: 0.46 in 200 mg dupilumab (Q2W) arm vs. 0.87 in matched placebo arm; 47.7% rate reduction in dupilumab arm compared to placebo ($P < 0.001$). Adjusted annualized exacerbation rate: 0.52 in 300 mg dupilumab (Q2W) arm vs. 0.97 in matched placebo arm; 46.0% rate reduction in dupilumab arm compared to placebo ($P < 0.001$)	100–160 ml improvement in FEV ₁ compared to placebo Change in pre-bronchodilator FEV ₁ from baseline (week 12): 320 ml in the 200 mg dupilumab arm vs. 180 ml in matched placebo arm (difference: 140 ml, $P < 0.001$); change in pre-bronchodilator FEV ₁ from baseline (week 12): 340 ml in the 300 mg dupilumab arm vs. 210 ml in matched placebo arm (difference 130 ml, $P < 0.001$)	NA NA	
		LIBERTY ASTHMA VENTURE, NCT02528214 [61]	59% reduction in rate of severe exacerbation compared to placebo	220 ml FEV ₁ improvement compared to placebo	Change in glucocorticoid dose: – 70.1% in dupilumab arm vs. – 41.9% in placebo arm ($P < 0.001$); dose reduction of at least 50%: 80% vs. 50%; dose reduction to less than 5 mg/day: 69% vs. 33%; complete discontinuation of oral glucocorticoid use: 48% vs. 25%	
Tezepelumab	TSLP	NCT02054130 [65]	61% reduction in exacerbation rate in 70 mg tezepelumab arm, 71% reduction in exacerbation rate in 210 mg tezepelumab arm, and 66% reduction in exacerbation rate in 280 mg tezepelumab arm compared to placebo	Improvement in pre-bronchodilator FEV ₁ in all tezepelumab arms compared to placebo	NA	

FE_{NO} fractional exhaled nitric oxide, FEV₁ forced expiratory volume in 1 s, IgE immunoglobulin E, IL-5 interleukin 5, IL-5R interleukin-5 receptor, IL-4R α interleukin-4 receptor alpha, IV intravenous administration, NA not available, OCS oral corticosteroid, Q2W once every 2 weeks, QAW once every 4 weeks, Q8W once every 8 weeks, SC subcutaneous administration, TSLP thymic stromal lymphopoietin

asthma symptoms, and reducing the need for steroid bursts while preventing the well-known adverse events associated with steroid use. Pivotal studies of the utilization of biological agents in patients with severe asthma are reported in Table 1, along with results concerning the main outcomes investigated.

MONOCLONAL ANTIBODIES IN SEVERE ASTHMA

Omalizumab

Omalizumab was the first biological drug to be approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of severe asthma [16, 17]. It is a recombinant humanized monoclonal antibody (mAb) that selectively binds circulating IgE, thus decreasing IgE levels in blood [18]. According to the recommendations of the Global Initiative for Asthma (GINA) and the EMA and FDA, omalizumab is indicated in adults and children ≥ 6 years old with IgE-mediated moderate-to-severe persistent allergic asthma that remains uncontrolled despite GINA step 4 treatment, high levels of blood IgE, and at least a sensitization to a perennial allergen [1]. Omalizumab is administered subcutaneously every 2–4 weeks according to the baseline total IgE level and body weight. Although the European label for omalizumab clarifies that the drug is suitable for long-term use, patients should be re-evaluated after 16 weeks of treatment to assess the efficacy of the drug before continuing with omalizumab therapy [19].

In a phase 3 randomized controlled trial (RCT) performed by Hanania et al. (NCT00314575), omalizumab reduced the rate of asthma exacerbation by 25% compared with placebo, improved the mean Asthma QoL Questionnaire score (AQLQS), reduced the daily as-needed rescue medication administered, and decreased the mean Asthma Symptom Score [20]. The EXTRA study (NCT00314574), a post hoc analysis of Hanania's RCT [20], grouped patients according to Th2 biomarker levels (high/low FeNO, blood eosinophils, and serum periostin levels) and demonstrated that the

reduction in exacerbation rate was greater in the groups with high biomarker levels [21]. This suggests that patients with high levels of Th2 biomarkers may receive a greater benefit from omalizumab therapy [21]. Other data showed that patients with at least 300 eosinophils/ μl obtained a better response from omalizumab treatment, with an up to 60% decrease in asthma exacerbations compared to patients with less than 300 eosinophils/ μl [22].

In the Inner-City Anti-IgE Therapy for Asthma (ICATA) phase 4 RCT (NCT00377572), omalizumab improved asthma control, reduced the use of as-needed rescue medication, and abolished seasonal exacerbation peaks in inner-city children, adolescents, and young adults (6–20 years old) with persistent allergic asthma compared with placebo [23].

It is well known that viral respiratory infections are a major cause of asthma exacerbations. Indeed, it has been demonstrated that induced airway hyperresponsiveness could be the result of bronchoconstriction caused by neureminidase via the inhibition of prejunctional muscarinic receptors (M_2 subtypes) [24]. Thus, it seems that the ability of omalizumab to reduce circulating IgE and the expression of the high-affinity IgE receptor Fc ϵ RI in DCs may attenuate the allergic response while strengthening the antiviral immune response, ultimately preventing exacerbations [25]. Further studies, including a meta-analysis, showed that treatment with omalizumab reduces the number of emergency department visits and the need for systemic steroid bursts [26–28].

The Xolair Persistency of Response After Long-Term Therapy (XPORT) long-term phase 4 RCT (NCT01125748) demonstrated that long-term therapy with omalizumab results in a persistent improvement in symptom control and a reduced risk of exacerbations. This study also showed that discontinuation of omalizumab is associated with increased circulating IgE levels and basophil expression of Fc ϵ RI [29]. However, an open prospective study demonstrated that the effects of 6 years of omalizumab may persist for at least 4 years after the discontinuation of therapy in 60% of patients [30].

In the phase 4 Real-life Effectiveness of Omalizumab Therapy (REALITY) study (NCT01776177),

a single-center, retrospective, observational, long-term, real-life investigation demonstrated that overall visit adherence upon treatment with omalizumab was 78%, although the adherence rate decreased by 20% every year [31]. The response to therapy rate was assessed via the Standardized Measure to Assess Response to Therapy (SMART) tool, according to which the response rate increased over time, with the highest level achieved after 5 years of treatment (85%) [31]. Omalizumab was well tolerated, with no serious AEs reported [31].

The phase 4 Real-life Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO; NCT01922037) proved that treatment with omalizumab reduces exacerbation and hospitalization rates and improves asthma symptom control irrespective of blood eosinophils and FeNO status at baseline. Indeed, these results contrast with those reported by Hanania et al. (NCT00314575), indicating that blood eosinophil count remains a controversial biomarker of omalizumab efficacy [32].

In the PROSPERO study, the frequency of serious AEs (SAEs) was 11.2% in both adolescents and adults. The most common serious AEs were asthma (3.2%), pneumonia (1.4%), chronic obstructive pulmonary disease (0.5%), anaphylactic events (0.5%), and pulmonary embolism and status asthmaticus (0.4%). All anaphylactic events were of moderate severity and related to omalizumab, and all occurred in the adult population. Seven fatal adverse events occurred, none of which was related to omalizumab [32].

Mepolizumab

Mepolizumab is a mAb that is directed against IL-5 and has been approved as an add-on treatment for patients ≥ 6 years old (EMA) or ≥ 12 years old (FDA) with severe eosinophilic asthma that remains uncontrolled despite GINA step 4 therapy [14, 33–35]. Mepolizumab is indicated in patients who have a blood eosinophil count of ≥ 150 cells/ μl at the moment of first administration or ≥ 300 cells/ μl in the past year and have had ≥ 2 asthma exacerbations

requiring steroid bursts in the previous year [34, 35]. In agreement with guidelines from the National Institute for Health and Clinical Excellence (NICE) in the UK, mepolizumab is indicated in patients with a blood eosinophil count of ≥ 300 cells/ μl or more in the previous 12 months and ≥ 4 asthma exacerbations requiring systemic steroids or continuous oral corticosteroids (OCSs) equivalent to (at least) prednisolone 5 mg/day over the previous 6 months [36]. Mepolizumab is administered subcutaneously at a fixed dose of 100 mg every 4 weeks.

Recommendations from international guidelines regarding the duration of treatment to assess the efficacy of mepolizumab are not consistent. For instance, the GINA document indicates that a 4-month trial should be adequate to assess the effectiveness of mepolizumab in patients with severe asthma [37], whereas the NICE guidelines suggest that mepolizumab should be stopped after 12 months of treatment if the asthma is not adequately controlled, or the treatment can be continued while assessing responsiveness to the drug each year [38].

In the DREAM (Dose Ranging Efficacy and Safety with Mepolizumab) phase 2 RCT (NCT01000506), mepolizumab significantly reduced the exacerbation rate and time to first exacerbation compared to placebo in patients with severe eosinophilic asthma with ≥ 300 blood eosinophils/ μl or sputum eosinophils $\geq 3\%$ ($P \leq 0.001$ for all tested doses: 75, 250, and 750 mg). Enhanced mepolizumab efficacy was detected in patients with an increased blood eosinophil count at baseline and a relatively high number of prior exacerbations [14].

In the MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) phase 3 RCT (NCT01691521), mepolizumab that was administered either intravenously (75 mg) or subcutaneously (100 mg) significantly reduced (by $\approx 50\%$) the asthma exacerbation rate in patients with severe eosinophilic asthma compared to placebo. Mepolizumab also improved the forced expiratory volume in 1 s (FEV₁) ($P < 0.05$ vs. placebo), the QoL assessed via the St. George's Respiratory Questionnaire (SGRQ), and asthma control assessed via the 5-item

Asthma Control Questionnaire (ACQ-5) (both $P < 0.001$ vs. placebo) [39].

In the SIRIUS (Steroid Reduction with Mepolizumab Study) phase 3 RCT (NCT01691508), which included patients with severe asthma requiring daily maintenance OCS therapy, mepolizumab reduced the dose of OCSs required by 50% while maintaining asthma control and reducing the exacerbation rate by 32% compared to placebo ($P < 0.05$) [40].

According to long-term efficacy and safety data on mepolizumab from the COSMOS study (NCT01842607), an extension study of the MENSA and SIRIUS RCTs, patients who were previously treated with mepolizumab maintained a reduced exacerbation rate whereas those who were in the placebo arms in the previous studies showed improvement at the same endpoints after mepolizumab administration [41]. Mepolizumab presented a positive long-term safety profile. No increase in the AE rate was observed over the study period or when compared with previous placebo-controlled trials. The most common AEs were respiratory tract infection (67%), headache (29%), worsening of the asthma (27%), bronchitis (21%), and injection-site reactions (12%). Systemic allergic/hypersensitive reactions were recorded in 2% of patients, and $< 1\%$ of patients experienced a nonallergic systemic reaction. No reports of mepolizumab-related anaphylaxis were reported. On-treatment opportunistic infections (7%) were also reported, none of which were parasitic infections. Malignancies were reported in 2% of patients [41].

The COLUMBA study (NCT01691859), an open-label, long-term extension study in patients who participated in the DREAM study, confirmed the long-term efficacy of mepolizumab at reducing the exacerbation rate, ACQ-5 and blood eosinophil counts, and the safety profile of this mAb [42].

The COSMOS Extension (COSMEX) study (NCT02135692) found that the long-term administration of mepolizumab was well tolerated and provided persistent clinical benefits in patients suffering from life-threatening or very severe eosinophilic asthma [43]. The annualized exacerbation rate was low (0.93 event/year), and patients who had previously participated in the

MENSA [39] and COSMOS [41] studies reported sustained reductions in the exacerbation rate and daily OCS use upon long-term treatment with mepolizumab [43]. Conversely, patients who interrupted therapy with mepolizumab for > 3 months between the COSMOS and the COSMEX studies reported an improvement in ACQ score and lung function as well as a reduction in eosinophil count when treatment with mepolizumab was restarted [43]. Twenty-five percent of the total population analyzed reported serious AEs, and 0.9% of those AEs were considered to be related to the treatment [43].

Reslizumab

Reslizumab is a mAb directed against IL-5, so it has the same mechanism of action as mepolizumab. It has been approved by the EMA and FDA as an add-on treatment for adult patients (≥ 18 years old) with severe eosinophilic asthma that remains uncontrolled despite therapy with high-dose ICSs plus another controller. Reslizumab is indicated in patients with ≥ 400 eosinophils/ μl and ≥ 3 asthma exacerbations in the past 12 months [36, 44, 45]. Reslizumab is administered intravenously every 4 weeks at a dose of 3 mg/kg.

Corren et al. [46], in a phase 3 RCT designed to establish the eosinophil threshold that should be used to select patients for reslizumab treatment (NCT01508936), demonstrated that treatment led to significant improvements in lung function, symptom control, rescue medication use, and forced vital capacity (FVC) in patients with ≥ 400 eosinophils/ μl . Two further phase 3 RCTs (NCT01287039, NCT01285323) demonstrated that reslizumab administered as an add-on therapy to ICSs with or without other controllers significantly reduced the asthma exacerbation rate compared to placebo (34% and 31% respectively; both $P < 0.0001$) [47].

An open-label extension study (NCT01290887) conducted by Murphy et al. [48] evaluated the safety and efficacy of reslizumab for up to 24 months and demonstrated that reslizumab-experienced patients and reslizumab-naïve patients had improved lung function and

asthma control throughout the study period. The most frequently reported AEs in both reslizumab-experienced and reslizumab-naïve patients were asthma worsening (28% vs. 46%), nasopharyngitis (14% vs. 14%), upper respiratory tract infection (10% vs. 9%), sinusitis (8% vs. 6%), headache (7% vs. 11%), and local administration-related AEs (< 1%). Anaphylaxis and parasitic and opportunistic infections were not reported. Similar levels of anti-reslizumab antibody were detected in patients in both groups at baseline (4%) and during treatment (5%).

Benralizumab

Benralizumab is a humanized afucosylated mAb against IL-5 receptor α (IL-5R α) that induces eosinophil apoptosis through the mechanism of antibody-dependent cell-mediated cytotoxicity (ADCC) involving natural killer cells, inducing peripheral blood eosinophil depletion [49, 50]. It is approved as an add-on treatment for inadequately controlled severe eosinophilic asthma in adult patients (EMA) and subjects aged ≥ 12 years (FDA) with ≥ 300 blood eosinophils/ μl [51, 52]. A 30 mg dose of benralizumab is administered subcutaneously every 4 weeks for the first 3 months and then every 8 weeks.

In two large phase 3 RCTs, SIROCCO (NCT01928771) and CALIMA (NCT01914757), which were carried out in patients with severe asthma and a high blood eosinophil count (≥ 300 cells/ μl), 30 mg of benralizumab administered as an add-on therapy every 4 weeks or every 8 weeks were found to significantly reduce the asthma exacerbation rate (by up to 51%; $P < 0.0001$) and to improve FEV₁ (by up to 159 ml) and the blood eosinophil count compared with the control [53, 54].

In the ZONDA phase 3 RCT (NCT02075255), OCS doses were reduced by 75% in the benralizumab arm, compared with 25% in the placebo arm, over 28 weeks of treatment. The annual exacerbation rate was reduced by 55% compared to placebo, but there was no change in FEV₁ [55].

In an extension study (NCT02258542), Busse et al. [56] demonstrated that benralizumab

administered for 2 years maintained its efficacy and had a safety and tolerability profile similar to that observed over 1 year in the SIROCCO and CALIMA RCTs. The most common AEs were viral upper respiratory tract infections (14–16%; mostly bacterial pneumonia) and worsening asthma (7–10%). No cases of helminth infection were reported, and rates of hypersensitivity AEs were similar across the study groups. Positive anti-drug antibody responses were detected in 8–11% of patients receiving benralizumab for a second year, but a slight decrease in eosinophil-depleting activity due to high titers of anti-drug antibodies was noted at very low trough concentrations of benralizumab [56].

Dupilumab

Dupilumab is a humanized mAb directed against the α chain of the IL-4 receptor (IL-4R α), which is common to both IL-4 and IL-13, so this drug is able to inhibit the signaling of both ILs. Dupilumab is approved by the FDA as an add-on maintenance therapy in patients with moderate-to-severe asthma who are aged ≥ 12 years and have an eosinophilic phenotype or OCS-dependent asthma, and by the EMA as an add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO in adolescents aged ≥ 12 years that is inadequately controlled with high-dose ICS plus another medicinal product for maintenance treatment.

Dupilumab is administered subcutaneously at an initial dose of 400 mg (two 200 mg injections) followed by 200 mg every 2 weeks, or at an initial dose of 600 mg (two 300 mg injections) followed by 300 mg every 2 weeks. According to the EMA, a starting dose of 600 mg is recommended only for patients with OCS-dependent asthma or moderate-to-severe atopic dermatitis (for which dupilumab is also indicated) [57]. The FDA approved both regimens (400/200 mg and 600/300 mg) without specific indications, except for patients with OCS-dependent asthma or moderate-to-severe atopic dermatitis, for whom an initial dose of 600 mg administered subcutaneously is indicated [58].

In a phase 2 dose-ranging study (NCT01854047), Wenzel et al. [59] allocated patients with severe uncontrolled asthma to four groups with different dosing and timing schemes (200 mg every 4 weeks, 300 mg every 4 weeks, 200 mg every 2 weeks, and 300 mg every 2 weeks). The dupilumab groups showed improved lung function and patient-reported outcomes as well as fewer severe exacerbations compared with placebo. Although these results were observed in the overall population, the subgroup with at least 300 eosinophils/ μl showed the greatest reduction in the annualized severe exacerbation rate and improvement in FEV₁ [59].

In the LIBERTY ASTHMA QUEST phase 3 RCT (NCT02414854) conducted in patients aged ≥ 12 years old with uncontrolled asthma, dupilumab significantly reduced asthma exacerbations by $\approx 50\%$ and improved FEV₁. Two dupilumab dosing schemes, 200 mg and 300 mg every 2 weeks, were tested [60]. In this study, the safety profile was favorable. The frequency of AEs was similar across the intervention groups (81.0%). Injection-site reaction was the most frequent AE (15.2% in the lower-dose dupilumab group vs. 5.4% in the matched placebo group; 18.4% in the higher-dose dupilumab group vs. 10.3% in the matched placebo group). An eosinophil count of > 3000 per cubic millimeter during the intervention period was considered to indicate an AE (AE rate: 1.2% in the dupilumab groups combined and 0.3% in the placebo groups combined). SAEs (worsening of hypereosinophilia and chronic eosinophilic pneumonia) were suffered by two patients in the dupilumab groups who showed increased blood eosinophils. Conjunctivitis was also observed during the study period, with no meaningful difference in rate between the study groups. The most frequent SAE was pneumonia (suffered by 8.2% of patients receiving dupilumab and 8.4% of patients receiving placebo). Persistent anti-drug antibody responses were reported, but they had no meaningful effect on drug safety or efficacy.

In the LIBERTY ASTHMA VENTURE phase 3 RCT (NCT02528214), Rabe et al. [61] demonstrated that dupilumab is effective at reducing the need for OCSs while maintaining asthma control, reducing asthma exacerbations (by

59.3%), and improving lung function. The frequency of AEs during the trial period was similar in the two groups (62% in the dupilumab group and 64% in the placebo group).

In a recent post-hoc analysis of a phase 2 study (NCT01854047), dupilumab produced a significant and clinically meaningful improvement in asthma symptom control as assessed via ACQ-5, AM/PM Asthma Symptoms Score, QoL, and productivity in an intention-to-treat population who received the drug administered at a dose of 200/300 mg every 2 weeks [62]. Another post-hoc analysis of the same study (NCT01854047) indicated that dupilumab 200 mg and 300 mg administered every 2 weeks significantly ($P < 0.05$) reduced the rate of severe exacerbations and significantly ($P < 0.05$) improved lung function, asthma control, and QoL compared to placebo, regardless of the exacerbation history of the patient [63].

According to a post hoc analysis of the LIBERTY ASTHMA QUEST study (NCT02414854), dupilumab administered at 200 mg and 300 mg significantly ($P < 0.001$) reduced the rate of severe exacerbations in uncontrolled, moderate-to-severe asthma patients with evidence of allergic asthma (-36.9% and -45.5% , respectively) and in patients without an allergic component (-60.0% and -44.6% , respectively) [64]. In patients with or without allergic asthma, both doses significantly ($P < 0.01$) improved asthma control as well as lung function compared to placebo [64]. Dupilumab 200 mg and 300 mg also significantly reduced total serum IgE compared to placebo in patients with asthma with or without an allergic component [64].

BIOLOGICAL DRUGS UNDER DEVELOPMENT

Tezepelumab is a humanized mAb that is under development. It binds TSLP, preventing the interaction of TSLP with its receptor, which is expressed on different immune cells of the type 2 inflammatory cascade. Corren et al. [65] conducted a phase 2 RCT (NCT02054130) that aimed to compare tezepelumab administered at 70 mg and 210 mg every 4 weeks and

tezepelumab administered at 280 mg every 2 weeks with placebo. All dosage regimens showed statistically significant reductions in the annualized asthma exacerbation rate and improvements in the pre-bronchodilator FEV₁ compared with placebo. Reductions in the investigated Th2 biomarkers (eosinophils, FeNO, and IgE) in patients treated with tezepelumab suggest that this mAb affects the IL-4, IL-5 and IL-13 pathways [65].

The drug-related SAEs observed in the RCT were pneumonia and stroke (which occurred in the same patient in the low-dose tezepelumab group) and Guillain–Barré syndrome (in the medium-dose tezepelumab group). Neither investigational product-related anaphylactic reactions nor the identification of neutralizing antibodies were reported [65].

Several studies that aim to evaluate the safety, tolerability, and efficacy profile of tezepelumab in adult patients with severe uncontrolled asthma are ongoing (CASCADE, NCT03688074; DIRECTION, NCT03927157; NAVIGATO, NCT03347279). A further phase 3 RCT will evaluate the glucocorticoid sparing effect of tezepelumab in adults with OCS-dependent asthma (SOURCE, NCT03406078).

DISCUSSION

The treatment approach for severe asthma has changed significantly during the past decade. Effective identification of specific biomarkers for severe asthma has become the basis for biomarker-related personalized medicine that has replaced the conventional strategy based on nonspecific drugs such as corticosteroids and bronchodilators—the so-called blockbuster drugs. The characterization of molecular targets has allowed the identification of patients with severe asthma who would benefit from specific biological treatments. Nevertheless, the class of biological agents that represent the best therapeutic option for patients with overlapping phenotypes is still unclear. Therefore, there is a need for further discriminatory biomarkers that can allow better patient selection and can be used to predict the response of the patient to targeted therapy. Furthermore, there is a lack of

direct comparisons between currently approved biological therapies. Thus, head-to-head RCTs and further network meta-analyses performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) and registered in the International Prospective Register of Systematic Reviews (PROSPERO) are needed to help clinicians to better identify the best biological therapy for each severely asthmatic patient [66].

Before starting treatment with a biological agent, it is necessary to correctly diagnose severe asthma and exclude possible confounding conditions that mimic asthma symptoms, namely chronic obstructive pulmonary disease (COPD), bronchiectasis, intermittent laryngeal obstruction (ILO), and hypersensitivity pneumonitis [67]. Comorbidities should also be assessed and eventually treated. The most frequent comorbidities associated with asthma include gastroesophageal reflux disease, aspiration, rhinosinusitis, obstructive sleep apnea, cardiovascular comorbidities, ILO, and infections [68].

The characterization of etiopathogenetic pathways defining the aspects of severe asthma has allowed the identification of specific biomarkers for specific phenotypes. Prognostic and therapeutic information can be obtained by focusing on these specific molecular targets. This approach may facilitate the effective treatment of this complex and heterogeneous disorder. The recent approval of novel biological agents has definitely changed the natural history of severe Th2-high asthma. Conversely, targeting the Th2 pathway in nonphenotyped patients seems to be barely effective.

In the GINA recommendations, biological therapy is suggested in patients with severe asthma who show typical biomarkers of type 2 airway inflammation. Currently recognized Th2-high asthma phenotypes include early- and late-onset forms of asthma. The early-onset allergic asthma phenotype is characterized by atopy, polysensitization to allergens, a high total IgE, high FeNO levels, high sputum and blood eosinophil counts, and increased airway periostin. Late-onset eosinophilic asthma is often characterized by CS treatment refractoriness and an association with chronic sinusitis

and nasal polyps. Blood eosinophils and FeNO are considered valid noninvasive alternative biomarkers to the detection of sputum eosinophil counts of $\geq 3\%$.

In order to identify the most effective and appropriate biological therapy to treat severe asthma, it is necessary to consider the therapeutic indications reported by international agencies, namely the EMA and FDA, as well as biomarkers (as predictors of response), although their role is often controversial. In this respect, Table 2 summarizes the indications for currently approved biological therapies for severe asthma treatment in terms of patient age, disease characteristics, posology, the main benefits, and the most common AEs, in agreement with the relevant EMA and FDA documents.

For patients with allergic non-eosinophilic severe asthma, high levels of blood IgE, and at least a sensitization to a perennial allergen, omalizumab should be considered the first-choice biological treatment. Conversely, for patients with eosinophilic nonallergic severe asthma, it is reasonable to add an anti-IL-5 biological agent to the standard therapy. Anti-IL-4R α is the treatment for severe eosinophilic type 2 asthma or patients requiring maintenance OCS [37].

Due to a lack of head-to-head comparison trials, there are currently no recommendations for choosing among all of the currently available biologics that target the IL-5 pathway. Therefore, despite being limited by differences in study design, several network meta-analyses have been conducted. In this respect, a matching-adjusted indirect comparison indicated that benralizumab and mepolizumab have similar efficacy profiles [69]. A network meta-analysis suggested that reslizumab could be more effective than benralizumab in patients with moderate-to-severe eosinophilic asthma, a high blood eosinophil count, and two or more exacerbations in the previous year [70]. Another indirect treatment comparison showed that, compared to reslizumab and benralizumab, mepolizumab reduced the risk of asthma exacerbations and improved disease control regardless of the blood eosinophil threshold [71]. In an arm-based network meta-analysis that aimed to assess the effects of monoclonal antibodies

on the rate of asthma exacerbation, there was no significant difference between the investigated agents [72]. Conversely, the results of another quantitative synthesis indicated that, although all current mAbs were effective at reducing the risk of exacerbation and improving FEV₁ compared to placebo, only dupilumab was significantly more effective than omalizumab at reducing the risk of exacerbation, and there was no difference between mepolizumab, reslizumab, benralizumab, and dupilumab [73]. Interestingly, dupilumab was also found to be significantly more effective than omalizumab, mepolizumab, and benralizumab at improving FEV₁, whereas omalizumab, mepolizumab, reslizumab, and benralizumab yielded similar improvements in FEV₁ [73].

According to the GINA recommendations, a 4-month trial should be conducted to assess asthma control. In the case of failed asthma control, it is possible to attempt to switch to a different type-2 targeted biological drug if the patient is eligible. Currently, only a few studies have been conducted on biological drug switching in patients with severe asthma. One of these, a 24-week prospective, multicenter, open-label, single-group, self-controlled study, showed that reslizumab significantly improved asthma control in patients with severe eosinophilic asthma and a poor response to omalizumab [74]. In the OSMO study, a multicenter, open-label, single-arm, 32-week trial, patients with severe asthma uncontrolled by omalizumab showed an improvement in asthma control after switching to mepolizumab [75]. Interestingly, this result was confirmed by real-world evidence [76]. Preliminary findings also suggest that in patients treated with mepolizumab who had poor asthma symptom control, switching to benralizumab led to improved QoL scores and reduced OCS maintenance doses [77]. Moreover, two triple-switch case reports indicate that patients show long-term responsiveness to mepolizumab after failed omalizumab therapy and bronchial thermoplasty [78]. However, how and when to switch from one biological drug to another and the treatment time at which the patient should be judged to be either a responder or nonresponder to therapy are yet to be adequately established.

Table 2 Approved biological therapies for severe asthma treatment: when, which, and for whom, in agreement with EMA and FDA documents

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Date of issue of marketing authorization and reference of product information	EMA 2005 [82] FDA 2003 [83]	EMA 2015 [35] FDA 2015 [34]	EMA 2016 [84] FDA 2016 [85]	EMA 2018 [86] FDA 2017 [87]	EMA 2019 [57] FDA 2017 [58]
Age of patients (when)	EMA: 6 years of age and older FDA: 6 years of age and older	EMA: 6 years of age and older FDA: 12 years of age and older	EMA: adult patients FDA: adult patients	EMA: adult patients FDA: 12 years of age and older	EMA: 12 years of age and older FDA: 12 years of age and older
mAb (which)	Humanized anti-IgE	Humanized anti-IL-5	Humanized anti-IL-5	Humanized anti-IL-5R α	Humanized anti-IL-4R α
Disease characteristics (for whom)	EMA: add-on treatment for IgE-mediated asthma with positive skin test or in vitro reactivity to a perennial aeroallergen, frequent daytime symptoms or night-time awakenings, multiple documented severe asthma exacerbations despite treatment with high doses of a ICS/LABA combination; reduced lung function (FEV ₁ < 80% predicted) in patients aged 12 years or over FDA: moderate to severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS	EMA: add-on treatment for severe refractory eosinophilic asthma FDA: add-on treatment for severe asthma with eosinophilic phenotype	EMA: add-on treatment for severe eosinophilic asthma inadequately controlled despite treatment with high-dose ICSs plus another medicinal product for maintenance treatment FDA: add-on treatment for severe eosinophilic asthma	EMA: add-on treatment for severe eosinophilic asthma inadequately controlled despite treatment with high-dose ICS/LABA combination FDA: add-on treatment for severe eosinophilic asthma	EMA: add-on treatment for type II severe asthma with increased blood eosinophils and/or raised exhaled nitric oxide inadequately controlled by high-dose ICSs plus another asthma medicinal product FDA: add-on treatment for moderate-to-severe eosinophilic asthma or oral corticosteroid-dependent asthma
Posology	75–600 mg in one to four subcutaneous injections every 4 weeks; the maximum recommended dose is 600 mg every 2 weeks	100 mg administered subcutaneously once every 4 weeks in adults and adolescents aged 12 years or over; 40 mg administered subcutaneously once every 4 weeks in children aged between 6 and 11 years	3 mg for each kg of bodyweight via intravenous infusion once every 4 weeks	30 mg by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter	An initial dose of 400 mg (two 200 mg subcutaneous injections) followed by 200 mg given every other week; an initial dose of 600 mg (two 300 mg subcutaneous injections) followed by 300 mg given every other week; for patients requiring concomitant oral corticosteroids or with comorbid moderate-to-severe atopic dermatitis for which dupilumab is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week

Table 2 continued

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Main benefits	Adults and adolescents: \approx 50% reduction in the number of exacerbations; improvement in quality of life and reduction in the use of ICS. Children: \approx 20% reduction in the number of exacerbations. Data are reported vs. placebo	Adults and adolescents: \approx 50% reduction in the number of exacerbations; about half of the patients reduced the daily dose of oral corticosteroid dose by more than 50% to a dose of 5 mg or less. Children: the reduction in eosinophil levels in the blood was comparable with that detected in adults. Data are reported vs. placebo	\approx 30% reduction in the number of exacerbations; improvement in lung function and asthma symptoms; decreased number of blood eosinophils. Data are reported vs. placebo	\approx 50% reduction in the number of exacerbations; \approx 30% reduction in the daily oral corticosteroid dose. Data are reported vs. placebo	\approx 50% reduction in the number of exacerbations; improvement in lung function; \approx 30% reduction in the daily oral corticosteroid dose. Data are reported vs. placebo
Most common adverse events	Patients aged 12 years or over: headache and injection site reactions. Children aged between 6 and 12 years: headache and pyrexia	Headache, injection site reactions, back pain	Increase in levels of the enzyme creatine phosphokinase in the blood, correlated with possible damage to muscles. Anaphylactic reactions may affect \leq 1% patients	Headache, pharyngitis	Infections, eye disorders (conjunctivitis and related conditions) and injection site reactions

EMA European Medicines Agency, FDA US Food and Drug Administration, ICS inhaled corticosteroids, IL interleukin, LABA long-acting β_2 agonist, mAB monoclonal antibody

Although a withdrawal from biological therapy could be attempted after at least 12 months of treatment to check whether asthma symptom control has been achieved with medium-dose ICS add-on therapy, there is currently limited evidence concerning the actual feasibility of biologic therapy cessation [29, 43].

Moreover, in patients with severe asthma that is uncontrolled despite receiving add-on therapy with a biologic agent, the use of combination biological therapy could be considered. However, the efficacy and safety profile of such a combination therapy in patients eligible for multiple mAbs has not been carefully studied; relevant data originate mainly from case reports [79].

Clinical trials of biological agents directed against IL-6, IL-17, or IL-33 in patients with Th2-low asthma phenotypes are ongoing, but current knowledge suggests that these subjects should be treated with chronic macrolide, bronchial thermoplasty, or imatinib [80]. Although important advances have been made, efforts are still needed to identify useful biomarkers for Th2-low severe asthma phenotypes and to define appropriate therapies for these patients.

CONCLUSIONS

The use of biological agents has revolutionized the management of severe asthma. Nevertheless, many patients with asthma remain inadequately controlled. Thus, further effort is needed to identify other potential molecular targets that could be used as prognostic and therapeutic biomarkers, as this will facilitate therapeutic strategies that are precisely tailored to each patient's requirements [81].

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