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Allergic and eosinophilic asthma in the era of biomarkers and biologics: similarities, differences and misconceptions

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Key Messages

- Allergic and eosinophilic asthma are both driven by type 2 (T2) inflammation, with eosinophils having a key role in the disease pathophysiology in each definition.
- Despite the substantial overlap between allergic and eosinophilic asthma, in terms of disease pathophysiology, two distinct definitions of allergic and eosinophilic asthma currently exist to define patient populations for clinical trials and treatment guidelines.
- The move to precision medicine requires the use of predictive biomarkers. In this review, IgE, as used in allergic asthma categorization, was not found to be a predictive biomarker of treatment responses to any biologic for severe asthma, whereas blood eosinophil counts, as an indicator of an eosinophilic phenotype, had utility in this regard.

Future studies are likely to refine severe asthma classifications by focussing on a biological, endophenotypic classification with combination biomarkers to help develop strategies to identify responders more precisely in the real-world. Such a personalized medicine-based approach to select the most appropriate biologic agent for individual patients will o

Abstract

Objective: Severe asthma is associated with substantial personal and economic burden; maintaining disease control is the key management goal. Increased understanding of asthma heterogeneity, and development of type-2 (T2) targeting biologics has significantly advanced disease management and outcomes;

however, despite both being driven by T2 inflammation, allergic and eosinophilic asthma have different treatment recommendations. We sought to better understand the similarities and differences between allergic and eosinophilic asthma and highlight where misconceptions may arise.

Data Sources: Published articles, pivotal trials, post hoc analyses, asthma clinical guidelines sourced from PubMed.

Study Selections: Sources reporting allergic and eosinophilic asthma classifications, disease mechanisms, biomarkers associated with treatment response.

Results: This review highlights that severe allergic and eosinophilic asthma are both driven by T2 inflammation with eosinophils playing a cardinal role. Despite this overlap, treatment recommendations differ based on asthma classification. T2 cytokine gene expression is a reasonably well-established research tool, but not a well-established biomarker in clinical practice, unlike blood eosinophil counts, fractional exhaled nitric oxide and immunoglobulin-E; the clinical relevance of immunoglobulin-E as a predictive biomarker remains unclear.

Conclusion: Asthma classifications that can be easily characterized at patient level to ensure accurate diagnosis, predict disease trajectory, and treatment response are required. The current dichotomy of allergic and eosinophilic asthma classifications is likely too simplistic, given the similar eosinophil-mediated disease pathophysiology in both classifications. Our results provide future directions to guide clinically meaningful interpretation of asthma endophenotypes, which may improve understanding of severe asthma characterization and aid future advances in defining responders more precisely with personalised medicine approaches.

Keywords (5/12): eosinophil, allergic asthma, biologic, biomarker, endotype

Abbreviations:

ACQ, Asthma Control Questionnaire

ACT, Asthma Control Test

AI, artificial intelligence

AQLQ, Asthma Quality of Life Questionnaire

ATS, American Thoracic Society

BD, bronchodilator

BEC, blood eosinophil count

CCL, chemokine ligand

CysLT, cysteinyl leukotrienes

EAACI, European Academy of Allergy and Clinical Immunology

ED, emergency department

EMA, European Medicines Agency

ERS, European respiratory Society

EU, Europe

FeNO, fractional inhaled nitric oxide

FEV₁, forced expiratory volume in 1 second

GINA, Global Initiative for Asthma

HRQoL, health-related quality of life

ICS, inhaled corticosteroid

Ig, immunoglobulin

IgE, immunoglobulin E

IL, interleukin

ILC, innate lymphoid cells

LABA, long-acting β_2 -agonist

MBP, major basic protein

n/r, not reported

n/s, not significant

OCS, oral corticosteroid

PAMPs, pattern-associated molecular pattern

PEF, peak expiratory flow

PGD, prostaglandin

ppb, parts per billion

R, receptor

SCS, systemic corticosteroid

SGRQ, St George's Respiratory Questionnaire

SPT, skin prick test

T2, Type 2

TGF, transforming growth factor

Th, T-helper

TSLP, thymic stromal lymphopoietin

US, United States

Introduction

Despite recent advances in asthma management, ~50% of patients with moderate-to-severe disease have uncontrolled symptoms despite adherence to inhaled corticosteroid/long-acting β_2 -agonist (ICS/LABA) therapy^{1,2}. Over the next two decades, asthma management is predicted to cost ~\$1 trillion in the USA

alone³. The severity and burden of asthma can be predicted by the presence of elevated blood eosinophil counts,⁴⁻⁷ with a ≥ 1.3 times higher risk of hospitalization in patients with asthma and blood eosinophil counts ≥ 150 cells/ μ L than in those with blood eosinophil counts below this threshold⁵.

The pathophysiology of severe asthma is complex,⁸ and as understanding of the disease has evolved, so too has diagnosis; traditional classification nomenclature has been replaced by definitions based on clusters of characteristics (phenotypes) and/or the underlying mechanisms of disease (endophenotypes/endotypes)^{9,10}. This approach provides precision medicine, whereby disease traits are identified through multidimensional assessment, and individualized treatment plans can be based upon these treatable traits for each patient, to optimize care¹¹.

Allergic and eosinophilic asthma are two distinct classifications, both mechanistically driven by type 2 (T2) inflammation, with elevated eosinophil counts being a common feature¹². While T2 inflammation-targeting biologics have changed the treatment landscape for severe allergic and eosinophilic asthma by improving symptom control in patients with poorly controlled disease,¹³⁻¹⁶ current guidelines make separate treatment recommendations for allergic and eosinophilic asthma,^{17,18} possibly based on a misconception that these classifications are distinct. Such misconceptions may be driven by population nomenclature from pivotal clinical trials. However, the considerable overlap between these phenotypic and endotypic patient populations¹⁹⁻²² challenges the stratification of patients in distinct allergic or eosinophilic asthma classifications.

This review highlights areas of overlap between severe allergic and eosinophilic asthma, weighs the merits of current biomarkers associated with treatment response, and provides potential future directions to guide clinically meaningful interpretation of asthma endophenotypes.

T2 inflammatory asthma

Allergic and eosinophilic asthma classifications

The most recent European Academy of Allergy and Clinical Immunology (EAACI) Biologicals Guidelines (2020) provide distinct definitions of allergic and eosinophilic asthma, noting that they are subsets of T2 high disease (**Table 1**)¹⁷. The clear distinction between allergic and eosinophilic asthma in these guidelines may be erroneous. Real-world studies in adults and children found that 22–56% of patients met the definition for both allergic and eosinophilic asthma classifications²⁰⁻²³. Furthermore, in a post hoc analysis of four clinical studies in adults with moderate-to-severe asthma, 76% (n=288) of 380 patients with eosinophilic disease (baseline blood eosinophil count ≥ 300 cells/ μ L) also met the study's definition of allergic asthma (allergen-specific immunoglobulin E [IgE] >0.35 kU/L)²³. IgE refers to a class of immunoglobulins thought to be important for host defense against parasitic diseases, in mast cell/basophil degranulation, antigen presentation, and allergic/atopic disease²⁴.

Cluster-based phenotyping and endo(pheno)typing approaches (**Table 2**), identify that allergic and eosinophilic traits overlap across clusters, suggesting frequent commonality rather than distinction with such labelling. Evidence from randomized controlled trials shows improved outcomes with biologics for patients with severe asthma (**Table 3**), although these studies may highlight redundancy for classical allergic markers in predicting treatment responses. For example, targeting eosinophilic inflammation with mepolizumab in severe asthma reduces the annual rate of clinically significant exacerbations versus placebo, irrespective of omalizumab eligibility, IgE levels (≤ 60 , >60 – 170 , >170 – 450 , >450 IU/mL) or atopic status (positive/negative based on ≥ 1 positive radioallergosorbent score ≥ 3 against five aeroallergens)²⁵. Similar observations were made in a pooled analysis of the CALIMA and SIROCCO studies, where patients with a baseline blood eosinophil count ≥ 300 cells/ μ L demonstrated improved annualized exacerbation rates, lung function, asthma control and

symptoms with benralizumab versus placebo, irrespective of omalizumab eligibility, the presence of atopy or serum IgE levels ($<150/\geq 150$ kU/L) ²⁶.

Together, these data highlight that allergic and eosinophilic asthma are not always mutually exclusive.

Mechanisms of T2 inflammation

Asthma is characterized by airway inflammation, propagated by a variety of key triggers, which results in bronchoconstriction, airway mucus plugging, and airway inflammation with potential remodeling (**Figures 1 and 2**) ¹⁸. Across both allergic eosinophilic and non-allergic eosinophilic disease, interleukin (IL)-9, IL-13 and cysteinyl leukotrienes, secreted by a range of inflammatory cell types, directly activate structural airway cells to promote smooth muscle contraction, increased vascular permeability, immune cell recruitment, and mucus hypersecretion, which can lead to fibrosis (**Figure 1**) ^{12, 27-32}. In allergic asthma, these changes are further compounded by mast cells and basophils releasing additional mediators including histamine, prostaglandin D2 and proteases ³³⁻³⁶. Across both allergic and non-allergic eosinophilic asthma, eosinophil-derived basic proteins are critical to changes in mucous cross-linking that underlies the tendency for airway mucus plugging, and are linked to sensory neural growth within the airways, together associated with decreased lung function. Furthermore, eosinophil-derived transforming growth factor- β and osteopontin augment airway remodeling ^{32, 37-39}.

Inter-immune cell signaling cascades, driven by epithelial cell-derived alarmins (thymic stromal lymphopoietin [TSLP], IL-33 and IL-25), further exacerbate the inflammatory environment (**Figure 2**) ¹². In allergic asthma, the TSLP-driven differentiation of allergen specific T-helper (Th) 2 cells promotes class switching of allergen-specific B cells to produce IgE antibodies, allowing for allergen-driven degranulation of mast cells and basophils ^{12, 30, 40}. In asthma with features of allergic and eosinophilic inflammation, cytokines secreted from mast cells and Th2 cells synergistically promote eosinophil recruitment to airway

tissue^{34, 36}. Once activated, eosinophils may present allergen-specific antigen to Th2 cells to further promote inflammation and the maturation, activation, and survival of eosinophils, mediated by IL-5³². In non-allergic eosinophilic disease, stimulated innate lymphoid cells (ILC)-2 cells secrete IL-5, and IL-13, compounding the eosinophilic inflammatory environment, but not driving IgE class switching, which is primarily driven by IL-4^{12, 27, 29, 32, 34}. While IgE and ILC2-driven mechanisms are predominant in traditional classifications of severe allergic asthma and severe eosinophilic asthma, respectively, eosinophils are highlighted as a convergent cell type for both contributing to the pathophysiology of disease and airway damage. Owing to the transient nature of signaling pathways, identifying eosinophils as a non-specific indicator of the upstream T2-signaling pathway for both asthma classifications circumvents labeling as one immutable endotype. This highlights the importance of a thorough understanding of the underlying endophenotype in individual patients, beyond classical asthma categorizations.

Biomarkers of biologic treatment response

The use of blood eosinophil counts, fractional exhaled nitric oxide (FeNO), and measures of airway T2 cytokine gene expression as successful biomarkers for patients with T2 inflammation is now well-established,⁴¹ and the suitability of these biomarkers in predicting biologic therapy treatment outcomes has also been explored (Table 5).

Specific and total IgE

Around 80% of patients with severe asthma have eosinophil counts ≥ 150 cells/ μ L and allergen-specific IgE levels >0.35 IU/mL^{22, 23}. This should not be surprising given that, in addition to IL-5, which promotes the recruitment, survival and activation of eosinophils, other co-drivers of the T2 inflammatory

cascade can promote B cell class switch and production of IgE (**Figure 2**). Nevertheless, the clinical relevance of total IgE as a biomarker of allergic or eosinophilic asthma is unclear. To date, neither baseline total nor specific IgE have demonstrated a predictive ability for responses to biologic treatment in either allergic or eosinophilic disease (**Table 5**). Consequently, the main clinical application for IgE currently is to facilitate omalizumab dosing, even though paradoxically IgE does not predict the likelihood of treatment response ⁴².

Blood eosinophil count

Despite different mechanisms of action, mepolizumab, benralizumab, dupilumab, and reslizumab treatment responses have been shown to be associated with elevated blood eosinophil counts (**Table 5**). Mepolizumab and dupilumab reduced exacerbation rates in patients with eosinophilic asthma and blood eosinophil counts ≥ 150 cells/ μ L ^{16, 43, 44}. Similarly, baseline blood eosinophil counts ≥ 300 cells/ μ L, in a subgroup of patients with severe uncontrolled asthma, were predictive of treatment responses to benralizumab. Across patients with severe uncontrolled asthma, a higher versus lower blood eosinophil count, especially ≥ 450 cells/ μ L, was identified to better predict benralizumab treatment responses, ⁴⁵ a trend that is observed for most asthma biologics. Likewise, reslizumab improvements in efficacy measures were greater in patients with baseline blood eosinophil counts ≥ 400 cells/ μ L than in those with blood eosinophil counts < 400 cells/ μ L ⁴⁶. It is important to note that these findings are based on isolated blood eosinophil counts prior to treatment, with recent studies demonstrating that these values may vary over time ^{47, 48}.

In patients with allergic asthma, the predictive capabilities of blood eosinophil count with omalizumab treatment are less clear (**Table 5**). In a clinical trial setting, blood eosinophil counts ≥ 260 cells/ μ L or ≥ 300 cells/ μ L may predict exacerbation rate reductions with omalizumab ^{49, 50}. However, real-world evidence is mixed. PROSPERO study results suggest that baseline blood eosinophil counts ≥ 300 cells/ μ L were not predictive of reduced exacerbations with

omalizumab, but may predict asthma control ¹⁴. In the STELLAIR trial, baseline blood eosinophil counts ≥ 300 cells/ μ L were unable to predict a reduction in exacerbation rates or improved symptom control with omalizumab ⁵¹. Together, these findings suggest that omalizumab may not be targeting eosinophilic inflammation in asthma, which is thought to be the major treatable trait underlying disease pathology and risk of exacerbation in severe asthma. Thus, whilst current guidelines from the global initiative for asthma (GINA, 2021) ¹⁸, European Respiratory Society/American Thoracic Society (ERS/ATS, 2019) ⁵² and EAACI (2020) ¹⁷ include elevated blood eosinophil counts as a predictor of response to anti-IgE as well as anti-IL-5/IL-5 receptor and anti-IL-4 therapies (**Table 4**), it is apparent that the strength of evidence is not equal across all biologics; other markers, such as FeNO may better predict the response to IL-13 targeted biologics, including dupilumab ¹⁸.

Markers of the IL-13 pathway: FeNO

In allergic and eosinophilic asthma, epithelial exposure to IL-13 induces nitric oxide synthase to increase production of nitric oxide, which can be measured by FeNO ⁵⁰. Analyses of clinical trial data in patients with allergic or severe uncontrolled asthma suggest baseline FeNO levels ≥ 19.5 parts per billion (ppb) or ≥ 25 ppb may predict responses to omalizumab or dupilumab treatment, respectively (**Table 5**) ^{43, 50, 53}. However, in an analysis of the DREAM study, little association was observed between intravenous mepolizumab treatment responses and FeNO levels ≥ 25 or ≥ 50 ppb ⁴⁴. Real-world data assessing FeNO as a potential biomarker for predicting response to biological therapies is also mixed (**Table 5**). Mepolizumab and benralizumab were effective independent of baseline FeNO levels in patients with severe eosinophilic asthma ⁵⁴. This may not be surprising given that these therapies precisely target IL-5, whereas FeNO production is instead promoted by IL-13-induced inflammation ⁵⁰. One small study in patients with severe asthma found that FeNO levels ≥ 25 ppb predicted responses to dupilumab in patients who had been unresponsive to omalizumab, mepolizumab, reslizumab, or benralizumab treatment ⁵⁵. In addition, a post

hoc analysis of the LIBERTY ASTHMA QUEST dupilumab trials found that higher baseline FeNO levels were associated with greater risk of severe asthma exacerbations, particularly in combination with baseline blood eosinophil counts ≥ 150 cells/ μ L and ≥ 2 prior exacerbations (**Table 5**)⁵⁶. Together, these findings indicate that FeNO has the necessary qualities of a clinically usable predictive biomarker.

Combinatorial biomarkers

Given the complexity of the T2 inflammatory pathways in allergic and eosinophilic asthma, the assessment of each potential biomarker in isolation may only represent part of the pathological picture. Indeed, over 70% of patients with severe asthma have ≥ 1 marker of T2 inflammation, including blood eosinophil count, total IgE or FeNO, with nearly 40% of patients exhibiting two markers⁵⁷. Some studies suggest that T2 inflammatory markers may work in synergy, as they have identified concomitant upregulation of T2 asthma biomarkers^{58,59}. Indeed, a recent analysis of pooled data from several trials across the spectrum of asthma severity found that blood eosinophil count and FeNO provided additive prognostic information on asthma exacerbation risk, with this risk increasing as FeNO level and blood eosinophil count increase⁶⁰.

In addition, a post hoc analysis of the DREAM and QUEST studies may indicate a predictive ability for a combination of a baseline blood eosinophil count and FeNO levels to predict treatment responses with mepolizumab and dupilumab (**Table 5**)⁴³. However, the predictive ability of these markers in conjunction with periostin is less clear (**Table 5**)^{50,61}. These data highlight the need for further research to determine whether these combinatorial biomarkers may have continued utility in predicting treatment responses to biologics. Nonetheless, data to date suggest potential for a more personalized approach, where treatment decisions are tailored to clinical features, specific elevated markers of T2 inflammation, associated comorbidities and how these factors impact both the activity and progression of disease.

The future of biomarkers in predicting treatment responses

Beyond the well-characterized biomarkers for predicting responses to biologic treatment in patients with allergic and eosinophilic asthma, additional potential biomarkers have been proposed. In an analysis of the SARP study in patients with exacerbation-prone asthma, each 1-pg/mL increase in baseline plasma IL-6 levels increased the incident asthma exacerbation rate ratio by 10% over the 3 years of follow-up⁶². These findings support other reports associating elevated IL-6 with greater disease burden in patients with asthma,⁶³⁻⁶⁵ and may lay a foundation for further investigation. In vitro studies have identified the IL4ra(R576) allele or Notch4 to be associated with severe asthma^{66, 67}; the impact of dupilumab in patients with the IL4ra(R576) allele will be explored in a double-blind, randomized, placebo-controlled parallel-group Phase IV clinical trial (NCT03694158)⁶⁸. Clinical characteristics, such as oral corticosteroid (OCS) use, comorbid nasal polyposis or pre-bronchodilator forced vital capacity <60% have also been proposed as clinically identifiable phenotypes indicative of differential treatment responses; a pooled post hoc analysis of the SIROCCO and CALIMA trials suggested combinations of these characteristics were associated with greater treatment response to benralizumab versus the total patient population, although the predictive ability of these clinical markers varied depending on whether exacerbation rates, lung function, or asthma symptom control was assessed¹³.

The identification of FeNO suggests that biological samples other than blood could be considered for biomarker identification, and other methodological approaches too. Initial and proof-of-concept studies suggest that metabolic profiling may identify disease signatures across respiratory diseases and in patients with food allergies^{66, 69, 70}. While this concept is emerging in the asthma field, an extension of this application could be considered for identifying potential biomarkers for biologic treatment response. A cardinal role has been established for eosinophils in asthma pathophysiology, but eosinophils are also thought to regulate metabolic homeostasis⁷¹. As such, a metabolomic methodological approach may have merit in identifying biomarkers. Proteomic analysis may

provide a further approach, with early studies starting to link novel biomarkers from sputum, serum, urine, bronchial fluid, and nasal lavage fluid to patients with asthma^{59, 72, 73}. In addition, there is an emerging area of imaging biomarker assessment to complement the biological and physiological biomarker assessments⁷⁴. Given the complexity and heterogeneity of asthma, and the increasing collection of datasets on potential biomarkers, artificial intelligence (AI), the use of advanced computer systems to perform tasks usually requiring human intelligence⁷⁵, could be explored to aid the identification, stratification and relevance of a multiple biomarker approach that can predict the likelihood of response with a biologic in future. Furthermore, AI could be used in conjunction with cluster analyses using a formula of mixed biomarkers weighted differently, to provide a better model for determining responses to specific biologic therapies. Indeed, intelligent asthma diagnosis is a trending topic and shows promise as an accurate method to identify patients with asthma based on biomarker variables⁷⁶.

When relying on biomarkers to predict biological treatment responses in patients with asthma, it is important to consider their limitations. Skin prick testing (SPT) is frequently used for specific IgE detection and illustrates atopic sensitization. However, the presence of atopy is not synonymous with allergic disease, where the atopic diathesis drives the disease process; this is noted in current guidelines¹⁸. Furthermore, atopic sensitization occurs in other atopic diseases, meaning a positive SPT could be discordant with the presence of asthma. Additionally, dependent upon the allergen, there may be a significant proportion of false positive findings, as suggested by discordance between epicutaneous and intradermal confirmatory testing⁷⁷. As such, there are recognized limitations with using SPT to define allergic disease and select patients for biologic therapy^{78, 79}. Nonetheless, atopic diseases do tend to develop together, and similar atopic triggers may play a role in multiple diseases,⁸⁰ as represented by the proportion of patients with allergic comorbidities across biological clinical trials for severe asthma (**Table 3**). Unsurprisingly, levels of biomarkers that complement the mechanism of action of a biologic therapy, such as blood

eosinophil counts in the case of anti-IL-5 agents, are reduced during treatment,^{53, 81-84} limiting their utility to pre-treatment only. Environmental and other clinical factors should also be considered; natural fluctuations in daily eosinophil count are observed in healthy participants and patients with eosinophilic asthma^{85, 86}; similar fluctuations in FeNO levels across the general population have also been noted⁸⁷. Other factors, such as OCS use, have been shown to influence both blood eosinophil count and FeNO levels^{18, 87-89}, therefore, using a single measurement may be suboptimal. Indeed, GINA 2022 guidelines recommend repeating blood eosinophil and FeNO testing up to three times¹⁸ and accordingly, over 80% of patients with severe asthma have historical eosinophil counts suggesting eosinophilic disease⁹⁰. Furthermore, baseline blood eosinophil count cut-offs established in trials in the western world may not be applicable to different patient populations,⁹¹ and median blood eosinophil counts in the general population have been found to be considerably lower (100–120 cells/ μ L) than previously thought⁸⁹. Despite these considerations, both blood eosinophil count and FeNO level testing are quantitative and are relatively non-invasive and simple methods to perform at regularly scheduled clinic visits⁹². Additionally, utilization of these tests can accurately identify patients at increased risk of exacerbations^{43, 56}, potentially reducing the need for future healthcare resource use. Together, the evidence on individual biomarkers and the emerging evidence for combinatorial biomarkers supports utilizing these markers to better predict biologic treatment responses in patients with asthma, in line with a drive towards personalized medicine.

Tezepelumab, a human monoclonal antibody that blocks thymic stromal lymphopoietin, has recently gained approval for the treatment of severe asthma. As per the other biologics in the same type 2 space, there is increasing benefit with tezepelumab in reducing exacerbations with increasing baseline blood eosinophils and FeNO but no predictive indication with total IgE⁹³. Studies have demonstrated efficacy in patients with lower peripheral blood eosinophils; however, to a lesser degree than those with higher peripheral blood eosinophil counts.

Conclusion

Ultimately, asthma classifications are needed that can be easily characterized on a patient level, be diagnosed accurately, predict disease trajectory, and give insight into the likelihood of a clinical response to treatment. Given that allergic and eosinophilic asthma have substantial overlap, with eosinophils featuring in and contributing to disease pathophysiology in both classifications, the dichotomy of allergic and eosinophilic asthma classifications is likely too simplistic. Currently, available data suggest that while IgE is not a predictive biomarker of treatment responses to any biologic treatment for severe asthma, blood eosinophil counts have utility in this regard and modelling with multiple biomarkers, with the help of AI where appropriate, may increase the predictive value. Future studies will refine severe asthma classification, but the direction of travel has been from severe asthma in general, to clinical phenotypes of severe asthma, including allergic asthma, towards mechanistic biomarker determined endophenotypes, such as eosinophilic (T2) asthma. The translation of endotypic classifications^{94, 95} and the application of “omics” strategies to understanding biologic therapy outcomes will further help define responders more precisely and aid therapeutic decision-making in severe asthma to look beyond the labels of allergic and eosinophilic asthma and ensure truly personalized medicine and optimal patient outcomes. Presently, further research to aid in selecting the most appropriate biologic agent for treating individual patients is desperately needed.

Trial Registration

not applicable

Authors' contributions

All authors were involved in the conception or design of the manuscript. JS was involved in the acquisition of data. All authors contributed to the analysis or interpretation of data, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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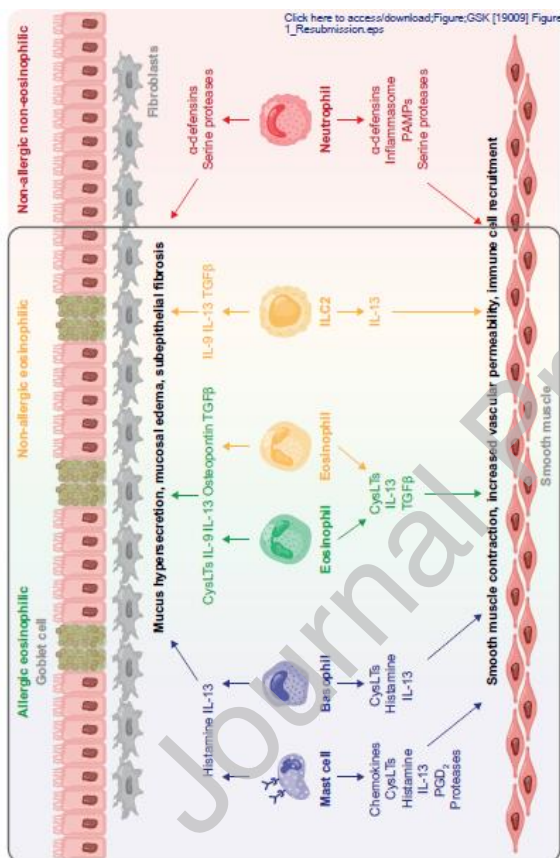
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Figure Legends

Figure 1. Fundamental immune pathways underpinning allergic and non-allergic eosinophilic asthma^{12, 27-40, 96, 97}.

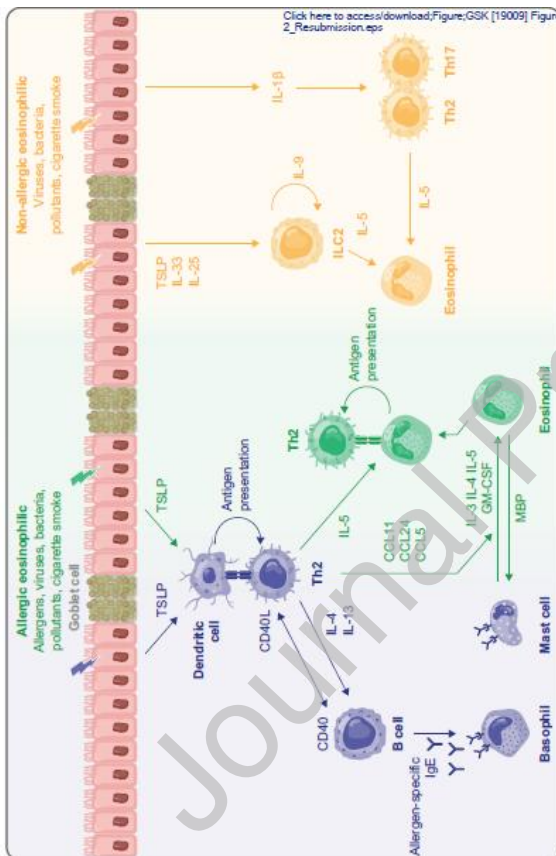
Figure 1



CysLT, cysteinyl leukotrienes; ILC2, type 2 innate lymphoid cells; IL, interleukin; PAMPs, pattern-associated molecular pattern; PGD, prostaglandin; TGF, transforming growth factor.

Figure 2. Immune cell signaling crosstalk underlies the inflammatory environment in allergic and non-allergic eosinophilic asthma ^{12, 27, 29, 30, 32, 34, 36, 40, 98}

Figure 2



CCL, chemokine ligand; CD, cluster of differentiation; GM-CSF, granulocyte-macrophage colony-stimulating factor; ILC2, type 2 innate lymphoid cells; Ig, immunoglobulin; IL, interleukin; MBP, major basic protein; Th, T helper; TSLP, thymic stromal lymphopoietin.

Tables

Table 1. European Academy of Allergy and Clinical Immunology (2020) Biologic Guideline definitions¹⁷ for allergic and eosinophilic asthma.

Asthma classification	Definition
T2 high	Sputum eosinophils ≥ 2 % and/or a blood eosinophil count ≥ 150 cells/ μ L and/or FeNO ≥ 20 ppb and/or asthma that is clinically allergen-driven and/or that requires maintenance OCS.
Allergic	Symptoms caused by exposure to a perennial aeroallergen and serum total IgE levels 30–1300 IU/mL not adequately controlled on ICS and/or other background controller(s).
Eosinophilic	Sputum eosinophils ≥ 1 % and/or a blood eosinophil count ≥ 150 cells/ μ L and/or FeNO ≥ 20 ppb.

FeNO, exhaled nitric oxide; ICS, inhaled corticosteroid; Ig, immunoglobulin; OCS, oral corticosteroid; ppb, parts per billion; T2, type 2.

Table 2. Overview of phenotyping, endotyping and endophenotyping studies for identifying subsets of asthma.

Study	Analysis parameters	Types of asthma subset identified	Evidence of elevated IgE levels	Evidence of elevated eosinophil count
SARP^{95, 99}	Patient demographics; asthma symptoms; medication use; healthcare utilization	5 clusters (N=726) 1: mild allergic; 2: mild-moderate allergic; 3: more severe older onset; 4: severe variable allergic; 5: severe fixed airflow	3 clusters had IgE >100 IU/mL (clusters 1, 2, and 4)	All 5 clusters had ≥ 150 cells/ μ L in blood; 2 clusters for sputum (clusters 3 and 4)
ADEPT¹⁰⁰	Airway T2 inflammation*; ACQ-7 score; age of disease onset; lung function	4 clusters (N=156) 1: mild, early onset, low inflammation; 2: moderate, highly atopic, eosinophilic; 3: mixed severity, non-eosinophilic, neutrophilic; 4: severe uncontrolled, missed granulocytic	All 4 clusters had IgE >100 IU/mL All 4 clusters had >70% of patients with IgE above >95% of healthy controls	3 clusters had ≥ 150 cells/ μ L in blood (clusters 1, 2, and 4); 2 clusters for sputum (clusters 2 and 4)
ADEPT¹⁰¹	Asthma severity	4 groups (N=150) Mild; moderate; severe; healthy controls	Elevated in all 4 asthma groups (p<0.05)	Elevated in all 4 asthma groups (p=0.0018)
U-BIOPRED⁸	Asthma severity;	2 clusters (N=606)	Elevated in both asthma	Elevated in both asthma

smoking status	Severe asthma-enriched; mixed cluster	clusters	clusters
* high/low based on C-C Motif Chemokine Ligand 26 bronchial biopsy gene expression.			

ACQ, asthma control questionnaire; Ig, immunoglobulin; T2, type 2.

Table 3. Impact of biologics in patients with severe asthma.

Biologic (study*)	Selected eligibility criteria	Baseline characteristics	Study primary outcome	Impact on outcome vs placebo				
				Exacerbations (number/rate/ patients)	Lung function	Symptoms	HRQoL	Daily OCS use
INNOVA TE¹⁰²	12–75 years of age; positive SPT to ≥1 perennial allergen; total serum IgE ≥30–≤700 IU/mL; ICS >1000 µg/day + LABA	Mean total IgE: 190–198 IU/mL Allergic comorbidity (%): n/r BEC: n/r Mean exacerbations [†] : 2.41–2.64	Rate of clinically significant [†] asthma exacerbations	Rate: ↓ 26% P=0.042	↑morning PEF P=0.042 Δ% predicted FEV ₁ : 2.8% P=0.043	↓total asthma symptom score P=0.039	ΔAQLQ: 0.45 p<0.001	n/r
Busse et al.¹⁰³	12–75 years of age; positive SPT to ≥1 perennial allergen; total serum IgE ≥30–≤700 IU/mL;	Mean total IgE: 173– 186 IU/mL Allergic comorbidity (%): n/r	Number of exacerbations	Number: ↓ 52–59% P=0.006	↑Morning PEF: 15 L/min Δ% predicted FEV ₁ : 4.3%	↓total asthma symptom score	n/r	n/r

	ICS 420–840 µg/day	BEC: n/r Exacerbations: n/r			P<0.019	P<0.01		
Solèr et al. ¹⁰⁴	12–75 years of age; positive SPT to ≥1 perennial allergen; total serum IgE ≥30–≤700 IU/mL; ICS 500–1,200 µg/day	Mean total IgE: 206– 223 IU/mL Allergic comorbidity (%): 77–78 BEC: n/r Exacerbations: n/r	Number of exacerbations	Number: ↓ 42–48% P<0.001	↑morning PEF p<0.01 Δ% predicted FEV ₁ : improved P<0.05	↓total asthma symptom score P≤0.01	n/r	↓200 µg/day p<0.00 1
Holgate et al. ¹⁰⁵	12–75 years of age; positive SPT to ≥1 aeroallergen; total serum IgE ≥30– ≤700 IU/mL; ICS ≥1000 µg/day	Mean total IgE: 266– 267 IU/mL Allergic comorbidity (%): n/r BEC: n/r Exacerbations: n/r	↓ fluticasone propionate dose	Rate: ↓ 35–45% P=n/s	Δpost-BD FEV ₁ : 89–116 mL P<0.05 (Week 4, 20, 28, 30)	↓total asthma symptom score P<0.05	↑AQLQ P<0.01	n/r
EXTRA ¹⁰	12–75 years of age; positive SPT to ≥1	Mean total IgE: 175–	Rate of asthma	Rate: ↓	n/r	↓ total asthma	↑AQLQ(S)	n/r

meponizumab	⁶	perennial allergen; total serum IgE ≥30–≤700 IU/mL; ICS ≥500 µg/day + LABA	179 IU/mL Allergic comorbidity (%): n/r BEC: n/r Mean exacerbations [§] : 1.9–2.0	exacerbations 25% P=0.006		symptom score: 0.26 P=0.038 [¶]	); 0.29 P=0.005	
	MENSA ¹⁰ 7	BEC ≥150 cells/µL [#] /≥300 cells/µL [§] ; ICS 880 µg/day + additional controller(s); ≥2 exacerbations requiring SCS [§]	Mean total IgE: 150– 180 IU/ml Allergic comorbidity (%): 48–50 BEC: 280–320 cells/µL Mean exacerbations [§] : 3.6–3.8	Rate of clinically significant [†] asthma exacerbations Rate: ↓ 53% P<0.001	↑Pre-BD FEV ₁ : 98 mL P=0.03 ↑Post-BD FEV ₁ : 138 mL P=0.004	↓ACQ-5: 0.44 P<0.001	↓SGRQ: 7.0 P<0.001	n/r
	MUSCA ¹⁰ 8	BEC ≥150 cells/µL [#] / ≥300 cells/µL [§] ; high-dose ICS +	Positive atopic status [#] : 45–46% Allergic comorbidity	Rate: ↓ 58% P<0.0001	Δ SGRQ total score ↑Pre-BD FEV ₁ : 120 mL p=0.001	↓ACQ-5: 0.4 P<0.0001	↓SGRQ: 7.7 P<0.0001	n/r

	additional controller(s); ≥ 2 exacerbations requiring SCS [§]	(%): n/r BEC: 300–350 cells/ μ L Mean exacerbations: 2.8							
	BEC ≥ 150 cells/ μ L [#] / ≥ 300 cells/ μ L [§] ; high-dose ICS + additional controller(s); ≥ 6 months maintenance OCS	Mean total IgE: 114–117 IU/mL Allergic comorbidity (%): 41–52 BEC: 230–250 cells/ μ L Mean exacerbations [§] : 2.9–3.3	$\downarrow$ OCS dose	Rate: $\downarrow$ 32% P=0.04	$\uparrow$ Pre-BD FEV ₁ : 114 mL P=0.15 $\uparrow$ Post-BD FEV ₁ : 128 mL P=0.06	$\downarrow$ ACQ-5: 0.52 P=0.004	$\downarrow$ SGRQ: 5.8 P=0.02	$\downarrow$ 50% P=0.007	
Resúmenes	Castro et al. ¹¹⁰ 12–75 years of age; screening BEC ≥ 400 cells/ μ L; ICS ≥ 440 μ g/day; ≥ 1 exacerbation requiring SCS [§]	Atopy/IgE: n/r Allergic comorbidity (%): n/r BEC: 610–696 cells/ μ L mean exacerbations [§] :	Rate of clinically significant [†] asthma exacerbations	Rate: $\downarrow$ 54% P<0.0001	$\uparrow$ FEV ₁ : 110mL P<0.0001	$\downarrow$ ACQ-7: 0.25 P<0.0001	$\uparrow$ AQLQ: 0.23 P<0.0001	n/r	

[illegible]

benralizumab	Pérez de Llano et al. ¹¹¹	18–70 years of age; BEC ≥400 cells/μL ; severe refractory asthma ^{**} ; history of omalizumab failure ^{††}	IgE: 105 IU/mL Allergic comorbidity (%): n/r BEC: 330 cells/mm ³ Median exacerbations [‡] : 1.0	Δ ACT	Patients: ↓ 52% P=n/r	↑ FEV ₁ : 200 mL P=0.195	↓ACQ-7: 0.5 P=0.004	↑AQLQ: 1.5 P<0.001	%↓20.4 P=0.019
	CALIMA ¹¹²	12–75 years of age; ICS >2500 μg/day + LABA; ≥2 exacerbations requiring SCS [§]	Atopy ^{††} (%): 63–65 Allergic comorbidity (%): n/r BEC: 350–370 cells/μL Mean exacerbations [§] : 2.7	Rate of asthma exacerbations	Rate: ≥300 cells/μL ↓ 28% P=0.0188 <300 cells/μL ↓40% P=0.0048	Pre-BD FEV ₁ : >300 cells/μL ↑116 mL P=0.0102 <300 cells/μL ↓15 mL P=0.7863	↓ACQ-6: >300 cells/μL: 0.25 P=0.0082 <300 cells/μL: 0.10 P=0.4488	↑AQLQ(S)+12: >300 cells/μL: 0.24 P=0.0194 <300 cells/μL: n/r	n/r
	SIROCC	12–75 years of age;	Atopy ^{††} (%): 57–61	Rate of asthma	Rate:	↑ Pre-BD FEV ₁ :	↓ACQ-6:	↑AQLQ(S)	n/r

dupumao	O¹¹²	medium-high -dose ICS + LABA; ≥2 exacerbations requiring SCS [§]	Allergic comorbidity (%): 54–55 BEC: 360–390 cells/μL Mean exacerbations [§] : 2.8–3.0	exacerbations	≥300 cells/μL ↓51% P<0.0001 <300 cells/μL ↓17% P=0.2685	≥300 cells/μL: 159 mL P=0.0006 <300 cells/μL: 102 mL P=0.568	≥300 cells/μL: 0.29 P=0.0028 <300 cells/μL: 0.22 P=0.1066	) +12: ≥300 cells/μL: 0.30 P=0.0036 <300 cells/μL: n/r
	ZONDA⁸³	BEC ≥150 cells/μL; medium- to-high-dose ICS/LABA [§] ; ≥6 months maintenance OCS	Atopy ^{ss} (%): 40–49 Allergic comorbidity (%): 40–55 BEC: 437–535 cells/μL	Δ OCS dose	Rate: ↓ 70% P<0.0001	n/r	↓ACQ-6: 0.55 P=0.001	↑AQLQ(S) +12: 0.45 P=0.004 ↓ 75% P<0.00 1
	LIBERT Y ASTHMA	≥12 years of age; GINA defined persistent asthma ≥12 months; ICS	Mean total IgE: 394– 461 IU/mL Atopy ^{ss} /allergic	Rate of asthma exacerbations Δ FEV ₁	Rate: ↓ 46% P<0.001	↑Pre-BD FEV ₁ : 130 mL p<0.001	↓ACQ-5: 0.22 P=n/r	ΔAQLQ(S): 0.26 n/r

QUEST⁵³	(≥500 µg/day) + additional controller(s)	comorbidity (%): 82 BEC: 349–391 cells/µL Mean exacerbations [§] : 2.02–2.09	P= n/r			
LIBERTY ASTHMA VENTURE¹¹³	GINA defined persistent asthma ≥12 months; ICS ≥500 µg/day + additional controller(s); SCS 5–35 mg ^{**}	Mean total IgE: n/r Allergic comorbidity (%): 77 BEC: 347 cells/µL Mean exacerbations [§] : 2.09	↓ OCS dose	Rate: ↓ 59% P: n/r	↑Pre-BD FEV ₁ : 220 mL P: n/r	↓ACQ-5: 0.47 P: n/r n/r P<0.001
LIBERTY ASTHMA VOYAGER¹¹⁴	6–11 years of age; GINA defined uncontrolled moderate-to-severe asthma; medium dose ICS + additional controller or high-dose	Median total IgE: 397–600 IU/mL Allergic comorbidity (%): 90–98 BEC: 520–740 cells/µL Mean severe		Rate: ↓ 54% P: n/r	↑% pre-BD FEV ₁ : 4.7% P: n/r	↓ACQ-7-IA: 0.28 P: n/r n/r ↓ 59–66% P: n/r

ICS +/- additional controller for ≥ 3 months with stable dose for ≥ 1 month; ≥ 1 severe exacerbation [§]	exacerbations [§] : 2.2–2.8	Rate of severe ^{##} asthma exacerbations
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Outcome data are shown for the approved dose of each biologic. *Clinical trials included based on ≥ 1 reported value for atopy/IgE or BEC at baseline; [†]previous 14 months; [‡]requiring SCS for ≥ 3 days, ED visit or hospitalization; [§]previous 12 months; [¶]P value did not meet the predefined $P < 0.025$ threshold specified in the type I error management plan; [#]at baseline; ^{||} ≥ 1 in the previous 3 years; ^{**}as defined by ERS/ATS guidelines; ^{††}assessed by persistent severe exacerbations and/or uncontrolled symptoms after ≥ 16 weeks of treatment and/or discontinuation of treatment due to adverse events; ^{‡‡}positive atopic status determine by positive skin test for ≥ 1 aeroallergen (house dust mite, dog dander, cat dander, alternaria); ^{26§§}definition of atopy not stated; ^{¶¶}previous 6 months; ^{##}requiring SCS for ≥ 3 days, hospitalization, or and ED visit leading to SCS use; ^{|||}annualized number of SCS courses.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; ATS, American Thoracic Society; BD, bronchodilator; BEC, blood eosinophil count; ED, emergency department; ERS, European respiratory Society; FEV₁, forced expiratory volume in 1 second; GINA, global initiative for asthma; HRQoL, health-related quality of life; IA, interviewer administered; ICS, inhaled corticosteroid; IgE, immunoglobulin-E; LABA, long-acting β_2 -agonist; n/r, not reported; n/s, not significant; OCS, oral corticosteroid; PEF, peak expiratory flow; SCS, systemic corticosteroid; SGRQ, St George's Respiratory Questionnaire; SPT, skin prick test.

Table 4. Guideline recommendations for biologic therapy use in the treatment of severe allergic and eosinophilic asthma.

	Target	GINA 2021 ¹⁸		ERS/ATS 2019 ³²		EAACI 2020 ¹⁷	
		Allergic	Eosinophilic	Allergic	Eosinophilic	Allergic	Eosinophilic
Omalizumab	IgE	Sensitization on SPT/specific IgE; prior exacerbation*	No specific recommendation	BEC ≥ 260 cells/ μ L; FeNO ≥ 19.5 ppb	No specific recommendation	Total IgE [†] ; ≥ 1 perennial aeroallergen	Diagnosis of severe persistent allergic asthma; BEC $\geq 260/\mu$ L; FeNO ≥ 24 ppb
Mepolizumab	IL-5	No specific recommendation	BEC $\geq 150/\geq 300$ cells/ μ L; prior exacerbation*	No specific recommendation	BEC ≥ 150 cells/ μ L; prior exacerbation; OCS-dependent patients	No specific recommendation	BEC ≥ 150 cells/ μ L [‡] / ≥ 300 cells/ μ L*
Reslizumab	IL-5	No specific recommendation	BEC $\geq 150/\geq 300$ cells/ μ L; prior exacerbation*	No specific recommendation	BEC ≥ 150 cells/ μ L; prior exacerbation; OCS-dependent patients	No specific recommendation	BEC ≥ 400 cells/ μ L
Benralizumab	IL-5R	No specific	BEC $\geq 150/\geq 300$ cells/ μ L;	No specific	BEC ≥ 150 cells/ μ L; prior exacerbation;	BEC > 300	BEC > 300 cells/ μ L

		recommendation	prior exacerbation*	recommendation	OCS-dependent patients	cells/ μ L or >150 cells/ μ L with atopy [†] and total IgE [‡]	or >150 cells/ μ L for OCS-dependent patients
Dupilumab	IL-4R	No specific recommendation	BEC $\geq$ 150 cells/ μ L or FeNO $\geq$ 25 ppb; prior exacerbation*; OCS- dependent patients	No specific recommendation	Recommended	BEC >150 cells/ μ L; FeNO >20 ppb	BEC >150 cells/ μ L; FeNO >20 ppb

*In the previous 12 months; [†]30–700 IU/mL (US) or 30–1500 IU/mL (EU); [‡]atopy based on positive Phadiatop test; [§]within a 2–4-week screening period; [¶]at initiation.

ATS, American Thoracic Society; BEC, blood eosinophil count; EAACI, European Academy of Allergy and Clinical Immunology; ERS, European Respiratory Society; EU, Europe; FeNO, exhaled nitric oxide; GINA, Global Initiative for Asthma; Ig, immunoglobulin; IL, interleukin; OCS, oral corticosteroid; ppb, parts per billion; R, receptor; SPT, skin prick test; US, United States.

Table 5. Selected biomarkers for patient responsiveness to biologics for severe asthma.

Therapy	Trial	Asthma classification	Outcomes assessed
Allergen specific IgE			
Omalizumab	Univariate analysis of INNOVATE ¹¹⁵	Allergic*	Number of (severe) exacerbations; responder analysis
Total IgE			
Omalizumab	Univariate analysis of 7 trials ¹¹⁶	Allergic [†]	Number and rate of (severe) exacerbations [‡] ; AQLQ score; physician's overall assessment
Omalizumab	STELLAIR ⁵¹	Severe allergic [‡]	physician's overall assessment; exacerbation [†] rate
Mepolizumab	Post hoc meta-analysis of MENSA and MUSCA ²⁵	Eosinophilic [§]	Exacerbation [†] rate; FEV ₁ ; S ₁ ACQ-5
Benralizumab	Pooled data from SIROCCO and CALIMA ⁴⁵	Severe uncontrolled	Exacerbation [†] rate
Dupilumab	Post hoc analysis of QUEST ¹⁵	Severe uncontrolled** ; allergic asthma ^{††} subgroup analysis	Exacerbation [§] rate; FEV ₁ ; A score
BEC			
Omalizumab	PROSPERO ¹⁴	Allergic [‡]	Responder analysis for exacerbations [‡] ; ACT score;
Omalizumab	Pooled data from 2 trials ⁴⁹	Allergic*	Exacerbation [†] rate
Omalizumab	Pre-specified and post hoc analysis of EXTRA ⁵⁰	Allergic*	Exacerbation [†] rate

Omalizumab	STELLAIR ⁵¹	Severe allergic [‡]	Physician's overall assessment; exacerbation [†] rate
Mepolizumab	Post hoc analysis of DREAM and MENSA ¹⁶	Eosinophilic [§]	Exacerbation [†] rate; FEV ₁ ; S; ACQ-5
Mepolizumab/ dupilumab	Post hoc analysis of DREAM and QUEST ⁴³	Eosinophilic [§]	Exacerbation [†] rate
Benralizumab	Pooled data from SIROCCO and CALIMA ¹³	Severe uncontrolled [‡] ; subgroup analysis in patients with BEC ≥ 300 cells/μL	Exacerbation [†] rate; FEV ₁ ; A
Benralizumab	Pooled data from SIROCCO and CALIMA ⁴⁵	Severe uncontrolled [‡]	Exacerbation [†] rate
Dupilumab	QUEST Post hoc analysis of QUEST ⁴³	Severe uncontrolled**	Exacerbation [§] rate; FEV ₁
Reslizumab	Pre-specified and post hoc clinical trial analyses ⁴⁶	Inadequately controlled ^{††}	FEV ₁ ; ACQ-7; SABA use; I; ACQ-6
FeNO			
Omalizumab	Pre-specified and post hoc analysis of EXTRA ⁵⁰	Allergic*	Exacerbation [†] rate
Mepolizumab/ benralizumab	Review of real-world evidence ⁵⁴	Severe eosinophilic [‡]	Exacerbation [†] rate; FEV ₁ ; O; ACQ-6 score; AQLQ score
Dupilumab	Post hoc analysis of QUEST ⁴³	Severe uncontrolled**	Exacerbation [§] rate; FEV ₁ ; as control
Dupilumab	QUEST ⁵³	Severe uncontrolled**	Exacerbation [§] rate; FEV ₁
Dupilumab	Real-world evidence ⁵⁵	Severe asthma ^{††} , with	ACT score; lung function; C

		previous antibody therapy ^{§§}	reduction
Placebo	Post hoc analysis of QUEST ⁵⁶	Severe uncontrolled**	Exacerbation rate [§]
BEC and FeNO			
Mepolizumab/ dupilumab	Post hoc analysis of DREAM and QUEST ⁴³	Eosinophilic [#]	Exacerbation [†] rate
Placebo	Post hoc analysis of QUEST ⁵⁶	Severe uncontrolled**	Exacerbation rate [§]
BEC, FeNO, and periostin			
Omalizumab	Pre-specified and post hoc analysis of EXTRA ⁵⁰	Allergic*	Exacerbation [†] rate
OCS	Single-blind, parallel-group, randomized controlled trial ⁶¹	Severe asthma ^{¶¶} with FeNO <45 ppb	OCS dose; ICS dose; exacerbation rate [‡] ; FEV ₁ ; ACQ-7 score; <i>λ</i> score

*Defined as positive SPT to ≥1 perennial allergen, total serum IgE ≥30–≤700 IU/mL;

[†]defined as worsening of asthma symptoms requiring SCS, or where severe exacerbations are specified, FEV₁ <60% personal best and requiring SCS; [‡]definition not specified in study;

[§]BEC ≥300 cells/μL in the previous year, or ≥150 cells/μL at screening; ^{§§}defined as worsening of asthma requiring SCS and/or an ED visit and/or hospitalization; [#]defined as BEC ≥300 cells/μL, sputum eosinophil count ≥3% or FeNO ≥50 ppb; [¶]defined as medium-to-high dosage ICS plus LABA and ≥2 exacerbations requiring SCS in the previous year; ^{¶¶}GINA defined persistent asthma ≥12 months and medium-to-high dosage ICS plus additional controllers;

^{††}despite use of medium dosage ICS; ^{‡‡}defined by the ERS/ATS consensus statement; ^{§§}anti-IgE, anti-IL-5 or anti-IL-5Ra therapy, as defined by the EMA prescription criteria; ^{¶¶}defined as treatment steps 4 and 5 (GINA).

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of

Life Questionnaire; ATS, American Thoracic Society; BEC, blood eosinophil count; ED, emergency department; EMA, European Medicines Agency; ERS, European respiratory Society; FeNO, exhaled nitric oxide; FEV₁, forced exhaled volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; Ig, immunoglobulin; LABA, long-acting β_2 -agonist; OCS, oral corticosteroid; ppb, parts per billion; SABA, short-acting beta agonist; SCS, systemic corticosteroid; SGRQ, St. George's Respiratory Questionnaire; SPT, skin prick test.