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Targeting the Inflammatory Cascade: The Evolution of Monoclonal Antibodies for Severe Asthma Management

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Abstract:

Background: Severe asthma affects approximately 5–10% of the asthma population and is characterized by significant heterogeneity in pathophysiology and clinical presentation. The condition is traditionally categorized into Type 2-high (T2-high) inflammation, driven by mechanisms such as eosinophilia and IgE mediation, and Type 2-low (T2-low) inflammation, which is less well-defined. Standard treatments involving broad immunosuppression with corticosteroids are often insufficient or associated with toxicity in severe cases. Consequently, the understanding of asthma has evolved from a "one-size-fits-all" approach to a precision medicine model based on specific phenotypes and endotypes.

Aim: The aim of this review is to examine the efficacy, safety, and selection of biological therapies for severe asthma.

Materials and Methods: The review included scientific papers sourced from the PubMed and Google Scholar databases.

Results: Monoclonal antibodies have transformed severe asthma management. Omalizumab addresses allergic asthma, while anti-IL-5 agents (mepolizumab, reslizumab, benralizumab) effectively reduce exacerbations in eosinophilic phenotypes. Dupilumab (targeting IL-4/IL-13) offers superior lung function improvement, particularly in mixed phenotypes. Notably, tezepelumab (anti-TSLP) and emerging anti-IL-33 agents demonstrate efficacy across a broader spectrum, offering new therapeutic options for previously refractory T2-low patients.

Conclusions: Biologics have shifted the therapeutic goal from disease control to clinical remission. While T2-high asthma is well-managed by existing targeted therapies, upstream inhibitors now provide vital solutions for the challenging T2-low population. Consequently, a precise, biomarker-driven approach is essential to select the optimal therapy and maximize patient outcomes.

Key words: severe asthma; omalizumab; dupilumab; mepolizumab; benralizumab; reslizumab; tezepelumab; astegolimab

Introduction:

Asthma is a prevalent and heterogeneous condition characterized by chronic airway inflammation, variable airflow obstruction, and bronchial hyperresponsiveness. The majority of patients achieve disease control with standard inhaled therapies such as inhaled corticosteroids (ICS) and inhaled long-acting bronchodilators (LABA). (Bell et al., 2014; Farinha et al., 2024). There is however a group of patients which suffer from severe asthma. It is is currently defined by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) as asthma that requires treatment with high-dose ICS plus a second controller (and/or systemic corticosteroids) to prevent it from becoming "uncontrolled," or which remains uncontrolled despite this therapy (Chung et al., 2022). It is estimated that severe asthma affects approximately 5–10% of the total asthma population (Bakakos et al., 2020).

Asthma is a complex syndrome driven by diverse pathophysiological mechanisms. This heterogeneity explains why traditional "one-size-fits-all" approaches, such as broad immunosuppression with corticosteroids, are often insufficient. In addition to that they can be associated with unacceptable toxicity in severe cases. The current understanding of severe asthma pathophysiology emphasizes the distinction between clinical characteristics (phenotypes) and the underlying molecular mechanisms (endotypes) (Rogers et al., 2023).

The current paradigm for asthma pathogenesis is the division into "Type 2-high" (T2-high) and "Type 2-low" (T2-low) inflammation. T2-high inflammation is the best-understood endotype and is prevalent in approximately 50–70% of severe asthma cases (Rogers et al., 2023). This pathway is orchestrated by T-helper 2 (Th2) cells and Group 2 innate lymphoid cells (ILC2s), which produce key cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). These cytokines drive the inflammatory cascade: IL-4 promotes immunoglobulin E (IgE) synthesis; IL-5 is crucial for eosinophil maturation, survival, and recruitment; and IL-13 contributes to mucus hypersecretion, airway hyperresponsiveness, and smooth muscle changes. (Vanbuul et al., 2015). Conversely, T2-low asthma is less well defined

but is often characterized by neutrophilic or paucigranulocytic inflammation, potentially driven by Th17 or Th1 pathways. It is frequently associated with corticosteroid insensitivity, obesity, and infection (Zervas et al., 2018).

The mutual interactions of these mechanisms result in distinct clinical phenotypes. The severe allergic asthma phenotype typically presents with early onset in childhood and is driven by allergen sensitization, mediated by IgE (Bakakos et al., 2020). In contrast, severe eosinophilic asthma is often characterized by adult onset, the presence of nasal polyps, and persistent airway eosinophilia despite corticosteroid treatment. Biomarkers such as blood eosinophil count (BEC), fractional exhaled nitric oxide (FeNO), and total serum IgE are now essential clinical tools used to identify these phenotypes and guide therapy. (Chung et al., 2022). Importantly, these phenotypes are not mutually exclusive. An "overlap" endotype exists where patients exhibit characteristics of both allergic and eosinophilic inflammation, making them eligible for multiple targeted therapies. Additionally there are other phenotypes, such as obesity-related asthma in which eosinophilic airway inflammation is not always present. (Desai et al., 2013; van Huisstede et al., 2014). Another phenotype worth mentioning is non-allergic asthma in which there is an increased number of neutrophils in the sputum and cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) are produced. In turn type 2 ILC2 is activated. (McKenzie et al., 2014). Those phenotypes represent different challenges often requiring different management strategies.

The discovery of these specific inflammatory pathways has revolutionized the management of severe asthma, moving the field from non-specific disease control toward precision medicine. The development of monoclonal antibodies that target specific upstream mediators of the T2 cascade, specifically IgE, IL-5, the IL-5 receptor, and the IL-4/IL-13 receptor, provides new hope for patients refractory to standard care. (Rogers et al., 2023). This review will examine the efficacy, safety, and selection of these biological therapies, addressing how phenotyping guides the choice of the right treatment for the right patient.

Research materials and methods

A comprehensive literature review was conducted using the PubMed and Google Scholar databases. The search focused on systematic reviews, meta-analyses, and key clinical trials published on the topic of biological treatment of severe asthma. To cover all relevant aspects, the search strategy included keywords such as "severe asthma" "biological treatment asthma" "omalizumab.", "dupilumab", "mepolizumab", "benralizumab" , "reslizumab", "tezepelumab" and "astegolimab".

Anti-IgE Antibodies

Omalizumab was the first biological agent approved for the treatment of asthma. It is a recombinant humanized monoclonal antibody designed to target circulating free Immunoglobulin E (IgE). By binding to the Cε3 domain of the IgE heavy chain, omalizumab prevents the interaction of IgE with high-affinity receptors (FcεRI) on mast cells and basophils (Pajno et al., 2020; Romano, 2015). This sequestration of free IgE subsequently leads to the downregulation of FcεRI expression on effector cells, thus inhibiting the release of inflammatory mediators responsible for the allergic cascade (Humbert et al., 2014).

The efficacy of omalizumab has been extensively documented in both adult and pediatric populations. It is currently indicated as an add-on therapy for patients aged six years and older with uncontrolled moderate-to-severe allergic asthma (Pajno et al., 2020). Clinical trials and real-world studies consistently demonstrate that omalizumab significantly reduces asthma exacerbations, hospitalizations, and the use of rescue medications (Romano, 2015). Furthermore, it allows for a reduction in inhaled corticosteroid (ICS) dosage and improves quality of life (Humbert et al., 2014). In pediatric populations specifically, omalizumab has

shown potential in reducing seasonal exacerbations, particularly those triggered by viral infections during the fall, potentially by restoring interferon-alpha responses (Sattler et al., 2017).

While originally restricted to IgE-mediated allergic asthma, there is evidence which suggests omalizumab's utility may extend to other phenotypes. In a 2022 study by Melscoet et al. omalizumab effectively reduced severe exacerbation rates in patients with non-atopic asthma and even those with T2-low profiles (non-atopic and non-eosinophilic). It was reported that in the non-atopic group, omalizumab reduced the severe exacerbation rate by 44% (95% CI 18-64%, $p<0.05$), 43% (CI 95% 20-60%, $p<0.05$), and 54% (CI 95% 36-67%, $p<0.05$), at 4, 6 and 12 months, respectively. Those results challenged the strict allergic indication for the use of omalizumab. (Melscoet et al., 2022). Additionally, structural airway changes influence treatment response. A study by Hanania et al. focused on patients with inadequately controlled allergic asthma aged 12-75 years old. A post-hoc analysis revealed that while omalizumab reduced exacerbations in patients with high bronchodilator responsiveness regardless of fixed airflow obstruction (FAO), improvements in lung function FEV1 were primarily observed in patients without FAO (Hanania et al., 2021). This suggests that while anti-IgE therapy mitigates inflammation-driven exacerbations across different remodeling profiles, fixed structural changes may limit functional lung improvement.

With the development of new biological therapies it is important to compare omalizumab with newer agents targeting the IL-5 and IL-4/IL-13 pathways. A target trial emulation compared omalizumab, mepolizumab, and dupilumab in patients with eosinophilic and allergic characteristics. The patients included were at least 18 years old and had baseline IgE levels between 30–700 IU/ml and peripheral eosinophils count were $\geq$150 cells/μL. The study found patients treated with dupilumab had a greater reduction in exacerbation rates and greater improvements in lung function compared to both omalizumab and mepolizumab. The adjusted incidence rate ratios were as follows: dupilumab vs. mepolizumab: 0.28, 95% , CI 0.09–0.84; dupilumab vs. omalizumab: 0.36, CI 0.12–1.09. (Akenroye et al., 2023). This suggests that for some patients which exhibit both allergic and eosinophilic traits, blockage of IL-4/IL-13 may offer superior clinical outcomes.

Anti IL-5/IL-5 receptor antibodies

The management of severe eosinophilic asthma has been revolutionized by the introduction of monoclonal antibodies targeting the interleukin-5 (IL-5) pathway and other type 2 inflammatory drivers. The efficacy of mepolizumab was established as early as 2012 The DREAM study was a pivotal randomized controlled trial. In this study 621 patients aged 12-74 with a history of recurrent severe asthma exacerbations were randomized to receive either placebo, 75mg, 250mg or 750mg of intravenous mepolizumab. Results showed that the drug significantly reduced the rate of clinically significant exacerbations across all doses, with the 75 mg dose demonstrating a 48% reduction ($p<0.0001$), 250 mg dose causing 39% reduction ($p=0.0005$), and the 750 mg dose showing a 52% reduction ($p<0.0001$) compared with placebo (Pavord et al., 2012).

While RCTs establish efficacy under controlled conditions, recent evidence highlights the translation of these benefits into heterogeneous real-world populations. A systematic review of real-world evidence involving 2,040 patients confirmed that mepolizumab treatment consistently reduced annualized exacerbation rates by 54% to 97% and allowed for OCS discontinuation in 27% to 84% of patients (Israel et al., 2021).

Evidence from the prospective REALITI-A study demonstrated that clinical benefits persist regardless of complex comorbidities. In a group of 822 patients with severe asthma and conditions such as gastroesophageal reflux disease (GERD), depression/anxiety, or chronic obstructive pulmonary disease (COPD), mepolizumab reduced clinically significant

exacerbations by 63% across all subgroups. It is worth noting that patients with chronic rhinosinusitis with nasal polyps exhibited a particularly favorable response, achieving a 75% reduction in exacerbation rates (Liu et al., 2023).

Comparative analyses of biological medications suggest subtle differences in outcome strengths. A Bayesian network meta-analysis comparing tezepelumab, dupilumab, benralizumab, and mepolizumab found that while all biologics improved outcomes over placebo, tezepelumab ranked highest for exacerbation reduction. Conversely, dupilumab was ranked most effective for improving pre-bronchodilator FEV1. Mepolizumab ranked highest for improving Asthma Control Questionnaire (ACQ) scores, though the results were not significantly different from tezepelumab (tezepelumab vs. mepolizumab, MD, 0.14, CI −0.10-0.38). However, it was noted that many statistically significant differences between these biologics fell below established minimal clinically important difference thresholds (Nopsopon et al., 2023).

The ultimate therapeutic goal in severe asthma is shifting from disease control to clinical remission. A post-hoc analysis of the REDES study proposed a multicomponent definition of treatment remission (exacerbation-free, OCS-free, and Asthma Control Test score ≥20). Following one year of mepolizumab treatment, 37% of patients achieved such remission, increasing from only 2% at baseline (Pavord et al., 2023). These findings suggest that for a significant group of patients, biological therapies can go beyond symptom management modifying the course of the disease.

Benralizumab is a humanized monoclonal antibody against IL-5 receptor α (IL-5Rα) which acts by depleting eosinophils and basophils from blood and mucosa in the airway. The pathway, although antibody-dependent, leads to cell-mediated cytotoxicity (Pham et al., 2016). The drug is indicated as an add-on therapy for uncontrolled severe eosinophilic asthma. Clinical trials have reinforced the efficacy and safety profile of benralizumab.

Lai et al. conducted a study on an Asian population of 695 patients aged 12-75 suffering from severe asthma. It was found that patients with a high baseline blood eosinophil count (≥300 cells/μL), benralizumab significantly reduced the annual asthma exacerbation rate by 74% compared with placebo (rate ratio 0.26, $p<0.0001$) (Lai et al., 2024). The benefits extend beyond exacerbation reduction, with benralizumab providing significant improvements in lung function and symptom control. In the high-eosinophil severe asthma group (n=473) included in this study, treatment significantly improved pre-bronchodilator FEV1 by a least squares difference of 0.25 L ($p<0.0001$) compared with placebo at week 48. Symptom control, measured by the total asthma symptom score, also improved with an LSD of -0.25 ($p=0.0126$). The therapy was well tolerated with a similar frequency of adverse effects observed in the benralizumab group (76%) and placebo (80%) (Lai et al., 2024).

However, another research suggests the role of eosinophils may be primarily inflammatory. In a study on mild allergic asthma, benralizumab achieved a significant attenuation of sputum eosinophilia after an allergen challenge (least squares mean difference -5.81%, $p=0.021$) but demonstrated no significant effect on the late asthmatic response (LAR) (Gauvreau et al., 2024).

Reslizumab is a humanized anti-interleukin 5 (IL-5) monoclonal antibody. It is specifically useful in patients with blood eosinophil counts of ≥400 cells/μL. IL-5 inhibition targets the maturation and survival of eosinophils, which causes airway inflammation. In two pivotal phase 3 trials, reslizumab (3.0 mg/kg intravenously every four weeks) significantly reduced the annual rate of clinical asthma exacerbations. Treatment resulted in a 50–59% reduction in the annual frequency of exacerbations compared with placebo (RR 0.50 and 0.41 in the respective studies; both ($p<0.0001$). Furthermore, reslizumab caused significant and

sustained improvements in lung function, with FEV1 improvements evident as early as week 4 and maintained through 52 weeks of treatment. (Castro et al., 2015).

Antibodies blocking the IL-4/IL-13 pathway

Dupilumab is a IgG4 monoclonal antibody that targets the interleukin-4 receptor alpha subunit (IL-4Rα). Unlike therapies that target specific cytokines (e.g., anti-IL-5), dupilumab inhibits the signaling of both IL-4 and IL-13, which are central drivers of Type 2 inflammation (Harb et al., 2020). By blocking the IL-4α subunit common to both the type I and type II receptor complexes, dupilumab prevents the activation of downstream STAT6 signaling pathways and reduces the expression of Type 2 inflammatory biomarkers, including fractional exhaled nitric oxide (FeNO), IgE, and eotaxin-3 (Moran et al., 2020; Harb et al., 2020).

The Phase 3 LIBERTY ASTHMA QUEST trial established the efficacy of dupilumab in uncontrolled moderate-to-severe asthma. 1902 patients aged 12 and older were divided into groups treated either with add-on subcutaneous dupilumab or placebo. Treatment resulted in a significant reduction in the annualized rate of severe asthma exacerbations, dropping by 47.7% (200 mg dose) and 46.0% (300 mg dose) compared to placebo ($p<0.001$). Improvements in lung function were rapid and sustained; at week 12, FEV1 increased by 0.32 L (200 mg) and 0.34 L (300 mg) over baseline. While efficacy was observed in the broad population, patients with elevated baseline biomarkers experienced the greatest benefit. For instance, patients with blood eosinophils ≥300 cells/mm³ experienced exacerbation rate reductions of 65.8% and 67.4% for the 200 mg and 300 mg doses, respectively (Castro et al., 2018).

Recent Phase 3 data from the Asia-Pacific region (China and India) are consistent with these findings. In patients with persistent asthma aged 12 or older, dupilumab improved FEV1 by a least squares mean difference of 0.31 L compared to placebo ($p<0.0001$) and reduced the risk of severe exacerbations by 62% ($p=0.002$) (Zhang et al., 2025). Furthermore, post-hoc analyses indicate that dupilumab is effective regardless of allergic status. In the QUEST cohort, severe exacerbation rates were reduced by 36.9–45.5% in patients with allergic asthma and by 44.6–60.0% in those without evidence of allergic asthma (Corren et al., 2020).

For patients with severe, oral corticosteroid (OCS)-dependent asthma, dupilumab provides the possibility for reducing their use and sparing the patient from corticosteroids' adverse effects.. Rabe et al. studied 210 patients with such dependency. It was reported that after 24 weeks the percentage reduction in glucocorticoid dose was 70.1% in the dupilumab group compared to 41.9% in the placebo group ($p<0.001$). Notably, 48% of patients receiving dupilumab completely discontinued oral glucocorticoids compared to 25% in the placebo group. Additionally the trial group was able to achieve a 59% reduction in severe exacerbations and a 0.22 L improvement in FEV1 (95% CI, 0.09 to 0.34) (Rabe et al., 2018).

Dupilumab is generally well tolerated. The most consistently reported adverse event across trials was injection-site reactions, occurring in 15–18% of patients in QUEST compared to 5–10% for placebo (Castro et al., 2018) and 5.0% vs 1.2% in the Asia-Pacific study (Zhang et al., 2025). A transient increase in blood eosinophil counts has been observed upon treatment initiation, likely due to the inhibition of eosinophil migration into tissues while bone marrow regress continues. In the VENTURE trial, transient eosinophilia was observed in 14% of dupilumab-treated patients compared to 1% in the placebo group (Rabe et al., 2018).

Antibodies Blocking Thymic Stromal Lymphopoietin (TSLP)

Tezepelumab is a human monoclonal antibody that targets thymic stromal lymphopoietin (TSLP). Unlike earlier biologics that target downstream effectors such as immunoglobulin E (IgE), interleukin (IL)-5, or the IL-4/IL-13 receptors, tezepelumab inhibits an upstream epithelial cytokine (Panettieri Jr et al., 2024). TSLP is released by airway epithelial cells in response to various environmental triggers, including allergens, viruses, and pollutants

(Caminati et al., 2024). Once released, TSLP acts on dendritic cells to promote the differentiation of naive T cells into Th2 cells, and simultaneously activates group 2 innate lymphoid cells (ILC2s), mast cells, and basophils. (Kurihara et al., 2023). By blocking the binding of TSLP to its receptor, tezepelumab broadly suppresses the inflammatory cascade, reducing levels of IL-4, IL-5, IL-13, and airway hyperresponsiveness. (Panettieri Jr et al., 2024).

The efficacy of tezepelumab has been established through major randomized clinical trials. In the NAVIGATOR trial 1061 patients aged 12 to 80 were randomized to either receive 210 mg of subcutaneous tezepelumab or placebo. The trial group demonstrated a significant reduction in the annualized asthma exacerbation rate. AAER was 0.93 in the tezepelumab group compared to 2.10 in the placebo group, representing a 56% reduction (rate ratio 0.44; 95% CI, 0.37 to 0.53). It is worth mentioning that while efficacy was highest in patients with high baseline blood eosinophil counts (BEC), statistically significant reductions were also observed in those with low type 2 (T2) biomarkers. In patients with BEC <300 cells/μL, the AAER was also reduced compared to placebo. (Menzies-Gow et al., 2021).

A pooled analysis of data from two double-blind placebo-controlled clinical trials further confirmed this broad efficacy. Overall among 1331 patients enrolled, tezepelumab reduced the AAER by 60% in the pooled population (rate ratio, 0.40; 95% CI, 0.34– 0.48) (Corren et al., 2023). Even in "triple T2-low" patients, defined as having low eosinophils (<150 cells/μL), low fractional exhaled nitric oxide (FeNO <25 ppb), and no perennial allergy, tezepelumab reduced exacerbations by 34% to 49% compared to placebo. (Panettieri Jr et al., 2024). This is another advantage of tezepelumab as other biologics generally show limited efficacy in T2-low phenotypes.

In addition to preventing exacerbations, tezepelumab improves lung function and airway pathology. In the NAVIGATOR trial, treatment resulted in a significant improvement in pre-bronchodilator FEV1 of 0.13 L over placebo at 52 weeks (Menzies-Gow et al., 2021). Mechanistic insights from the CASCADE study revealed that tezepelumab significantly reduced airway submucosal eosinophils by 89% compared to 25% with placebo (Kurihara et al., 2023). Furthermore, exploratory analyses showed that tezepelumab reduced the occlusive mucus plug score by a mean of 1.7 points compared to no change in the placebo group. It suggests a capacity to remodel airway mucus pathology (Nordenmark et al., 2023).

The SOURCE study evaluated the oral corticosteroid (OCS) sparing effect of tezepelumab. While the primary endpoint of statistically significant OCS reduction was not met in the overall population, a favorable trend was observed in patients with higher baseline eosinophils (≥150 cells/μL), suggesting that TSLP inhibition may be less effective for OCS reduction in strictly non-eosinophilic, OCS-dependent patients (Kurihara et al., 2023). In terms of safety, tezepelumab was well tolerated in most trials. Adverse event rates were generally similar to placebo. Common adverse effects included nasopharyngitis and pharyngitis. (Menzies-Gow et al., 2021; Corren et al., 2017)

New biological targets (IL-33 pathway)

The interleukin-33 (IL-33) pathway is a promising target for severe asthma therapy. It might be particularly useful for patients who do not respond optimally to existing type 2 (T2)-targeted biologics. IL-33 is an epithelial-derived "alarmin" released in response to environmental triggers such as allergens, pollutants, and viruses (Kelsen et al., 2021). It binds to the ST2 receptor (IL-1 receptor-like 1) on various immune cells, including innate lymphoid cells type 2 (ILC2s), mast cells, and eosinophils. As a result inflammatory cascades associated with both T2 and non-T2 asthma phenotypes are initiated (Kotani et al., 2022).

Astegolimab is a fully human IgG2 monoclonal antibody that selectively inhibits the ST2 receptor. By blocking ST2, astegolimab prevents extracellular IL-33 from binding to its receptor complex, thereby inhibiting the downstream release of pro-inflammatory cytokines

like IL-4, IL-5, and IL-13 (Kelsen et al., 2021). Unlike therapies that target downstream cytokines (e.g., IL-5 or IL-4), blocking the IL-33/ST2 axis targets the inflammation further upstream (Calderon et al., 2023). An advantage of this mechanism is that ST2 is expressed on cells involved in broad inflammatory pathways, including those driving non-eosinophilic disease.

The efficacy of astegolimab was evaluated in the Phase 2b ZENYATTA trial. It included 502 adults with uncontrolled severe asthma. They were randomized to receive subcutaneously every 4 weeks either placebo or astegolimab in the following doses: 70mg, 210mg, 490mg. As a result the biologic significantly reduced the AAER 37% (p=0.01), 22% (p=0.18) and 43% (p=0.005) with the increasing dosage compared to placebo. Crucially, astegolimab demonstrated efficacy in patients with low biomarkers of T2 inflammation, a population with limited therapeutic options. In a group of patients with low blood eosinophils (≤300 cells/μL), the 490 mg dose reduced the AER by 54% (p=0.002). On the other hand, the treatment did not significantly reduce exacerbations in patients with high eosinophil counts (≥300 cells/μL) (Kelsen et al., 2021). This suggests the biologic's utility for T2-low phenotypes which are often refractory to other biologics. Further research is required to confirm these findings and establish the role of IL-33 blockade in the treatment of severe asthma.

While astegolimab targets the receptor, other biologics target the IL-33 ligand itself. Itepekimab (anti-IL-33) has demonstrated benefits for lung function and asthma control. However it is currently being prioritized for COPD in Phase 3 trials. Another agent, tozorakimab, showed potential benefits for early-onset eosinophilic asthma in Phase 2a trials (Faria et al., 2025).

Conclusions:

Introducing biologics was the most significant advance in the management of severe asthma. Endotyping and phenotyping of the condition has led to the development of highly effective biological agents. Those therapies, including omalizumab, the anti-IL-5 pathway drugs (mepolizumab, reslizumab, benralizumab), and dupilumab, have consistently proven their ability to dramatically reduce exacerbation rates, improve lung function (FEV1), and achieve meaningful OCS sparing effects. Dupilumab, in particular, offers a powerful option for the allergic-eosinophilic overlap phenotype by simultaneously blocking both IL-4 and IL-13 signaling, leading to superior outcomes in certain clinical comparisons.

Newly developed biologics can now be successfully used to address the challenging T2-low subset of severe asthma patients. Tezepelumab targets an upstream epithelial-derived alarmin that initiates the inflammatory cascade regardless of T2 biomarker status. The evidence supporting tezepelumab's broad efficacy, extending into patients with low eosinophil counts, firmly establishes it as a vital option for previously refractory T2-low disease. Furthermore, the early promise of new targets like the IL-33 pathway, specifically with agents such as astegolimab (anti-ST2), suggests further therapeutic options for non-eosinophilic inflammation. The focus of clinical management is shifting from mere disease control toward achieving clinical remission. The growing availability of targeted therapies now necessitates a biomarker-driven approach to selecting the most appropriate agent for each patient.

Disclosure

Author's contributions

Conceptualization:ES;
Methodology:VP, ES;
Software:ES;Check:VP;
Formal analysis:VP
Investigation:ES,VP

Resources:ES,VP
Data curation:VP;
Writing-rough preparation:ES
Writing-review and editing:ES,VP
Supervision:ES

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