



# Evidence-based answers to clinical controversies in the management of severe asthma

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## Abstract

Asthma is a chronic inflammatory airway disorder characterized by recurrent symptoms, airflow obstruction, and bronchial hyperresponsiveness. Approximately 5–10% of asthma cases are classified as severe, requiring high-dose inhaled corticosteroids (ICS) plus additional controllers, often including systemic corticosteroids. Severe asthma imposes a substantial burden on patients due to frequent exacerbations and reduced quality of life. The pathophysiology of severe asthma involves distinct phenotypic and endotypic variations, primarily classified into high-type 2 (T2) and low-T2 inflammatory profiles. While high-T2 asthma, encompassing eosinophilic and allergic subtypes, benefits from targeted biologic therapies such as monoclonal antibodies against interleukin-5 (IL-5), IL-4/IL-13, thymic stromal lymphopoietin (TSLP), and IgE, treatment options for low-T2 asthma remain limited. The advent of precision medicine has facilitated the identification of novel biomarkers for severe asthma, guiding therapeutic decisions and enabling disease stratification. However, key clinical challenges remain, including selecting the most effective biologic therapy, optimal treatment duration, and safe de-escalation strategies upon achieving remission. This review explores the latest evidence on biological therapies, their immunomodulatory effects, and their potential role in reversing bronchial remodelling. Additionally, it discusses emerging biomarkers that may predict treatment response and remission, ultimately contributing to a more personalized approach to asthma management.

## Keywords

Severe, biological, airway, eosinophilic, asthma, remodelling, biomarkers

## Introduction

Asthma is a chronic inflammatory disorder of the airways characterized by variable and recurrent symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. Asthma affects approximately 300 million individuals worldwide and poses a significant public health burden due

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to its impact on quality of life and healthcare costs [1]. The pathophysiology of asthma involves a complex interaction of genetic, environmental, and immunological factors, resulting in airway inflammation and remodeling [2].

Approximately 17% of asthmatics suffer from “difficult-to-treat asthma”, where poor control is attributed to factors such as suboptimal adherence to treatment, incorrect inhaler technique, smoking, or comorbidities like gastroesophageal reflux, chronic rhinosinusitis, obesity, and obstructive sleep apnea [3]. Severe asthma (SA), a subset of difficult-to-treat asthma, affects about 5–10% of the total asthma population. It is defined by the need for high-dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite the high level of treatment [4]. This subset of patients experiences frequent exacerbations, persistent symptoms, and significant limitations in daily activities, often requiring intensive management and specialized care [5]. They need treatment with high-dose ICS plus a second controller with/without oral corticosteroids (OCS).

Despite confirmation of the diagnosis and adequate treatment of comorbidities and confounding factors, such as inhaler technique, adherence, risk factors, and triggers (allergens, air pollution, respiratory infections, and tobacco smoking), the desired outcome is usually not achieved [3]. Multiple phenotypes of SA have been identified, including type 2 (T2; high-T2 and low-T2) (Table 1).

**Table 1. Key distinguishing features between type 2 (T2) and no-T2 or low-T2 asthma**

High-T2 asthma	Type no-T2 or low-T2 asthma
Associated with eosinophilic inflammation	Associated with neutrophilic or pauci-granulocytic inflammation
Driven by Th2-type cytokines (IL-4, IL-5, IL-13)	Driven by other inflammatory pathways (e.g., IL-17, IL-8)
Often has elevated IgE levels	IgE levels are usually normal or low
More likely to be responsive to corticosteroids	Often resistant or less responsive to corticosteroids
Common in allergic asthma and late-onset eosinophilic asthma	Common in obese patients, smokers, and the elderly
Biomarkers: FeNO, blood eosinophils, periostin	Biomarkers: none well established or under investigation
Targeted by biologic therapies (e.g., anti-IL-5, anti-IL-4R)	Few targeted treatments are currently available
Often diagnosed via biomarker analysis	Diagnosis often relies on clinical assessment and exclusion

FeNO: fractional exhaled nitric oxide; IL-4: interleukin-4

High-T2 asthma is a subtype of SA characterized by a high level of T2 inflammation. This inflammation is primarily driven by eosinophils and allergic responses. High-T2 asthma includes early-onset allergic asthma, late-onset eosinophilic asthma (EA), and non-allergic asthma with aspirin-exacerbated respiratory disease (AERD) [6]. Elevated levels of eosinophils in the blood and sputum are associated with increased asthma severity, exacerbation rate, and airway remodeling [7]. T2 asthma represents approximately 70% of SA cases [8]. On the other hand, low-T2 phenotypes are related to obesity, the elderly, and/or smoking [9]. This phenotype is characterized by a predominance of neutrophilic or paucigranulocytic cellular infiltrates [10]. Currently, no biological therapy is approved for low-T2 asthma, but clinical trials with agents targeting interleukin (IL)-17 are ongoing [11].

The mechanisms involved in the development of asthma could be several and change over time.

Targeted therapies, such as monoclonal antibodies against IL-5 and its receptor, anti-IgE, anti-thymic stromal lymphopoietin (TSLP), and anti-IL-4/IL-13 have shown efficacy in reducing eosinophilic inflammation and improving clinical outcomes in patients with severe EA [12].

Early intervention and personalized treatment strategies are essential for effective management of SA. Identifying specific biomarkers and phenotypes can guide the selection of targeted therapies, optimizing patient outcomes and reducing the disease burden [13]. The integration of molecular diagnostics and precision medicine approaches is promising for advanced asthma management and improving the quality of life in SA patients [14].

Clinical remission is emerging as an important and ambitious goal in asthma management [15], and is a composite endpoint often defined as meeting 3 to 4 key pillars (control of asthma symptoms, optimization/stabilization of lung function, no exacerbations, and no OCS use) over a set period of time [16], and may include the role and definition of biological remission, such as low-T2 biomarkers or normal airway responsiveness [17]. However, its definition remains under construction.

In clinical settings where SA is treated, physicians often face challenges in translating scientific evidence into effective patient management. These difficulties are primarily due to the complex process of applying research findings to real-world practice. Clear, evidence-based answers to common clinical questions are therefore essential to guide asthma care. To address this need, a bibliographic review was conducted in PubMed, focusing on the most widely cited studies and established asthma management guidelines. This review aims to explore current controversies and unresolved questions in the management of SA with biological treatments, including the role of novel biomarkers and strategies for treatment de-escalation following disease remission.

## Questions, controversies, and unmet needs

### Could we compare the efficacy among biologic treatments in high-T2 profiles?

Some studies have compared the efficacy of biological treatments for SA, either directly or indirectly. Although their methodologies and population characteristics may vary, these studies are crucial for identifying the most effective treatments for different patient subgroups. Presented below are representative studies demonstrating these comparisons.

#### Direct comparison studies

Scientific studies directly compare different biological medications for treating SA in real-world settings [18–20]. Several multicenter retrospective studies have evaluated the efficacy of various biological drugs in patients with SA for at least 12 months. Despite differing data collection methods, the results were generally comparable, with differences based on the drugs included in each study. Although the methods of data collection varied, the studied objectives and their results allow for conclusions about the populations studied.

#### Indirect comparison studies

These studies use data from existing randomized controlled trials (RCTs) and apply statistical methods for indirect comparisons to obtain comparable results across treatments. A common approach is matched-adjusted indirect comparisons (MAIC), where patient data from one trial are adjusted to match characteristics from another trial, allowing for a more balanced and accurate comparison [21]. Results vary, demonstrating differing efficacies among biologics across populations [22–24].

#### Systematic reviews and meta-analyses

These are powerful tools for comparing the efficacy of different biological treatments by combining multiple trials; these analyses provide comprehensive efficacy and safety data. Kyriakopoulos et al. [25], analyzed 48 RCTs of approved biologic agents for SA (16,350 participants), showing biologics significantly reduced exacerbations, hospitalizations, and corticosteroid use, with modest improvements in lung function, asthma control, and quality of life, although heterogeneity among studies was noted.

#### Network meta-analysis

Network meta-analysis (NMA) extends traditional meta-analyses, integrating direct (head-to-head comparisons) and indirect (comparisons via a common comparator) evidence to compare multiple treatments simultaneously [26]. NMAs are powerful tools for comparing multiple biological treatments in SA, providing a more complete and robust view of the relative efficacy and safety of these treatments compared to traditional systematic reviews. Provide relevant information to identify differences among biologics for SA and guide clinical decision-making, in defined clinical scenarios and proposed objectives [27–30].

Due to the lack of extensive comparative studies, there are currently no recommendations for selecting the appropriate treatment among those available. Therefore, the choice is empirical and likely shared between doctor and patient, with previously defined treatment objectives. [Table 2](#) summarises the comparative methods described.

**Table 2. Comparative methods between biologics for SA**

Method	Description	Key findings
Direct comparison studies	Scientific studies that directly compare different biological medications for treating SA in real-world settings.	These studies generally show that all biological drugs improve various objectives, including the frequency of exacerbations, use of systemic corticosteroids, and asthma control.
Indirect comparison studies	These studies use data from existing randomized controlled trials (RCTs) and apply statistical methods for indirect comparisons, such as matched-adjusted indirect comparisons (MAIC).	They demonstrate variable results with a predominance of the efficacy of one biologic over another in different patient populations.
Systematic reviews and meta-analyses	These studies compile and analyze data from multiple clinical trials, providing a comprehensive view of treatments' relative efficacy and safety.	They allow a more precise estimate of the treatment effect by increasing the sample size and statistical power. Significant heterogeneity was found in the effect estimates across subgroups and endpoints.
Network meta-analysis (NMA)	NMA extends traditional meta-analyses, allowing for the simultaneous comparison of multiple treatments, even when direct comparisons in clinical trials do not exist.	They provide a comparative view of the efficacy and safety of different biologics for treating SA, integrating data from multiple clinical trials.

SA: severe asthma

### How long should biological treatment be maintained?

According to GINA 2021, a treatment duration of at least 4 to 6 months is recommended to assess the response to biological treatment in patients with SA, followed by re-evaluation every 3–6 months [3, 31]. Current international guidelines generally recommend continuing biologic therapy for a minimum of 12 months before considering a withdrawal attempt. Such a decision should only be contemplated if the patient's asthma remains well controlled while receiving, at a minimum, a maintenance regimen that includes medium-dose ICS [1].

If there is no clinically meaningful improvement after 4 to 6 months of treatment with a biologic agent, switching to an alternative biologic with a different mechanism of action should be considered, provided that the eligibility criteria are still met [32]. For patients with incomplete responses, add-on therapy with a second biologic may be considered, but this indication is not currently supported by robust evidence from randomized clinical trials or by international guidelines, and it is not considered a recommended standard practice. This option can be considerably expensive and is usually not covered by insurance companies or healthcare systems.

The duration of biological treatment for SA depends on several factors, including the patient's response to therapy, disease severity, control of comorbidities, use of OCS, and the presence of clinically relevant side effects.

### Clinical response

The primary factor in determining the biological treatment duration is the patient's clinical response. If the patient shows significant improvement in symptoms, reduced exacerbations, and better lung function, treatment should be continued. Regular monitoring and assessment are essential to evaluate the ongoing effectiveness of the therapy and the achievement of the objectives proposed by physicians and patients.

In recent years, response levels to biological treatments have been established to categorize patients who respond spectacularly, partially, or inadequately to therapy. Although several definitions of clinical response or remission have been proposed, a "clinical response" generally includes a reduction in the annualized exacerbation rate, reduction of OCS dose, and improvement of lung function without clinical bronchial symptoms. Some authors define "clinical remission" as the complete absence of exacerbations and the need for OCS, well-controlled symptoms, and stabilization of lung function [33]. In September 2023

[34], ACAAI, ATS, and AAAAI postulated six mandatory criteria to be reached within one year for clinical remission in asthma: no exacerbations, no missed work or school over 12 months due to asthma-related symptoms, stable and optimized pulmonary, treatment with ICS only at low-medium doses, an asthma control test (ACT) score of > 20 or an asthma control questionnaire (ACQ) score of < 1.5, and symptoms requiring one-time reliever therapy no more than once a month.

A study from the Danish Severe Asthma Register cohort reported that 79% of patients had a clinical response and 19% achieved clinical remission [35]. Certain clinical characteristics were associated with a higher probability of achieving remission, such as earlier initiation of biological therapy (patients with shorter disease duration), fixed airflow obstruction and remodeling, mild forms of the disease, and minimal or no use of OCS. Complete remission goes beyond clinical remission and is defined as the absence of underlying inflammation and structural changes in the airways, demonstrated by negative bronchial hyperresponsiveness [36]. Complete remission should not be defined in asthma patients who still require treatment to control their disease. Another issue is that patients with long-standing disease and/or significant loss of lung function, usually with fixed airway obstruction, cannot achieve all the criteria for a clinical response, even if they meet the other criteria. Predictors of remission include younger age, better previous asthma control, lower previous ICS dose, milder airway hyperresponsiveness (AHR), fewer nasal polyps, and lower levels of blood neutrophils [37]. Remission, as a disease state, should be differentiated from the concept of a super-responder, which refers specifically to the degree of response to treatment [34].

Quantitative assessments of airway function using chest computed tomography (CT) and magnetic resonance imaging (MRI) in clinical trials of tezepelumab (NCT05280418), benralizumab (NCT03976310), and dupilumab (NCT0440318) aim to enhance the understanding of remission in SA by evaluating both large and small airways, as well as mucus plugging scores [38–40]. These imaging-based metrics may support the development of new treatment endpoints.

Although clinical response is a desirable goal, some patients may accept marginal improvements in disease expression and fear losing the benefits obtained during the initial biological treatment.

The NICE guidelines recommend that benralizumab, mepolizumab, and reslizumab be reviewed after 12 months of treatment and discontinued if asthma has not responded adequately [31, 41, 42]. For dupilumab, the NICE guideline recommends interruption if the rate of SA exacerbations has not been reduced by at least 50% after 12 months [43].

#### Disease severity

Patients with severe, persistent asthma may require long-term biological treatment to maintain symptom control and prevent exacerbations. The decision to continue treatment should be based on disease severity and the risk of exacerbations if treatment is discontinued.

#### Use of corticosteroids

For patients chronically treated with OCS, reducing the OCS dose is an important consideration and a primary goal of biological treatment in SA [44]. Cessation of maintenance OCS is a major criterion for clinical remission [45].

#### Control of comorbidities

The ISAR group identified chronic rhinosinusitis, with or without nasal polyposis, as a potential predictor of a positive response to biologics, particularly in reducing exacerbation risk, improving asthma control, and enhancing lung function. Obesity is a common comorbidity associated with poorer asthma control, increased risk of exacerbations, impaired lung function, and reduced quality of life [46].

#### Side effects

The presence of side effects may influence the duration of biological treatment. If a patient experiences significant adverse effects, the healthcare provider may consider adjusting the dosage or switching to an

alternative therapy. Long-term side effects are unknown, but their presence appears anecdotal [47]. A long-term safety review, conducted after over a decade of experimental studies and validated by real-world clinical experience, has not indicated any increase in malignant diseases, such as solid tumours or leukaemia, among patients undergoing treatment [48]. After 5 years of starting treatment with benralizumab, the MELTEMI study confirmed ongoing safety with rates of malignancy and serious infections at less than 2% [49].

### Biomarkers

Monitoring biomarkers of high-T2 asthma, such as blood and/or sputum eosinophil counts and fractional exhaled nitric oxide (FeNO) levels, can help guide the duration of treatment [50]. A sustained reduction in these biomarkers may indicate that the treatment is effective and should be continued. High levels predict the risk of more severe exacerbations, poor disease control, and poor response to treatment [51]. Serum IgE is a marker of atopy, but not useful in monitoring response to biological therapies [52].

Anyway, the duration of biological treatment should be individualized based on the patient's specific needs and circumstances. A personalized approach ensures that the treatment is tailored to achieve the best possible outcomes for each patient. Most SA patients treated with biologic therapies continue in the long term, with only 13% stopping them and 16% switching to another biologic [53].

### Once remission of SA is achieved, how do we de-escalate treatment?

Once remission of SA is achieved, the approach to de-escalating treatment should be carefully planned to maintain disease control while minimizing medication use. De-escalation of treatment should be gradual and closely monitored. If the patient is on biological therapy and has achieved remission, the decision to reduce or discontinue biologics should be based on clinical assessment and biomarkers. Some patients may be able to reduce the frequency of biologic administration or switch to a lower dose. However, complete discontinuation should be approached with caution and only considered if the patient has been stable for an extended period. Abrupt discontinuation of biologics or inhalers can lead to a relapse of symptoms. Elevated levels of FeNO after suspension of long-term therapy with omalizumab could predict near-exacerbation [54]. The COMET Study evaluated the effects of stopping versus continuing long-term mepolizumab therapy on asthma control [55]. Patients who stopped mepolizumab had an increased risk and shorter time to first asthma worsening compared to those who continued, largely driven by worsening in rescue medication use and morning PEF. Similar results were observed in another study after a 12-month follow-up following mepolizumab discontinuation [56]. Interestingly, patients who stopped treatment for 3 months between the COSMOS and COSMEX studies showed improvement in ACQ score, lung function, and eosinophil count when therapy was restarted [57].

A step-down protocol for SA patients treated with omalizumab has been published [58]. Patients must have received omalizumab treatment for at least one and a half years, the OCS dose must have reached the lowest tolerated dose, and lung function tests must be equal to or better than at entry. Then, omalizumab can be reduced by half and halved again every 6 months if the patient is clinically stable. Around one-third of the patients tolerated omalizumab withdrawal safely, and this benefit was long-lasting. French authors propose maintaining continuous therapy with omalizumab for a minimum of two years, after which discontinuation may be considered in patients with inactive allergic disease, low peripheral eosinophil counts, reduced FeNO levels, well-controlled asthma, and no history of severe exacerbation for at least one year [59]. A phase 4 study, XPORT, demonstrated persistent improvement in asthma control and reduced risk of exacerbations in patients treated with omalizumab. In this study, the interruption of the therapy could increase IgE levels and basophil expression of FcεRI [55]. In real-life experience, the effects of 6 years of omalizumab treatment may persist for at least 4 years after discontinuation in 60% of asthmatic patients [60].

ICS, long-acting bronchodilator agents (LABAs), long-acting muscarinic antagonists (LAMAs), and leukotriene inhibitor (LI) are often the basis of SA maintenance therapy. Once remission is achieved, the ICS dose can be gradually reduced while monitoring for any signs of worsening symptoms. LABAs should

generally be continued as part of a combination therapy with ICS to maintain control. LAMAs and LI can also be withdrawn while monitoring asthma progression. Regular follow-up appointments are essential to monitor the patient's response to treatment adjustments. Spirometry, peak flow measurements, and assessment of symptoms (validated questionnaires: ACT [61], ACQ [62], global evaluation of treatment effectiveness (GETE) [63], Saint George's Respiratory Questionnaire (SGRQ) [64]) should be conducted to ensure asthma control is maintained. GINA recommends reducing ICS doses in patients with SA who respond positively to biologics [3]. In the randomized, multicenter, open-label, phase 4 study (SHAMAL), patients who received at least three doses of benralizumab were studied to analyze the effect of ICS reduction. Ninety-two percent of patients successfully reduced their high-dose ICS. However, patients need at least a low-to-moderate dose of ICS to control asthma. These results are important because some patients may experience early benefits, leading them to believe they can reduce ICS, which can increase the risk of exacerbations and poor asthma control.

The education of the patient about the importance of adherence to the adjusted treatment plan and recognizing early signs of exacerbation is crucial. Patients should be instructed on how to use their medications correctly and when to request medical assistance.

Each patient's treatment plan should be individualized based on their specific needs, asthma severity, and response to previous treatments. Biomarkers such as blood eosinophil counts and FeNO levels can help guide the de-escalation process.

### **New biomarkers for SA**

While phenotyping/endotyping asthma and identifying relevant biomarkers offer opportunities to target treatments toward the underlying causes of the disease, there are also challenges and issues associated with using precision medicine via biomarkers [65]. These challenges partly explain why biomarker measurements are not yet routinely used in clinical practice. Blood and/or sputum eosinophils, FeNO, and serum total IgE are the most widely used biomarkers for the diagnosis of both high-T2 and low-T2 asthma in clinical practice. Currently, there is a significant lack of biomarkers predictive of disease remission and safe step-down of treatment. There are several new biomarkers, both in high-T2 and low-T2, are being investigated for the monitoring of SA. These biomarkers can help in understanding the disease's pathophysiology, in the prediction of risk of exacerbations, and in tailoring personalized treatment strategies. Here are some of the emerging biomarkers.

YKL-40 is a chitinase-like protein that is elevated in patients with SA. It is associated with airway remodeling and inflammation, making it a potential biomarker for disease severity and progression. YKL-40 promotes allergen sensitization, IgE production [66], bronchial smooth muscle cell proliferation, and bronchial remodeling [67]. A systematic meta-analysis showed that the level of YKL-40 was significantly higher in asthmatic patients than in the normal group, regardless of age and residential location, and it also increases with severity and acute exacerbation ( $p < 0.05$ ) [68]. Some studies linked YKL-40 to high-T2 inflammation [69] and others to severe neutrophilic and obesity-associated asthma [70]. YKL-40 has low specificity, as high levels are also found in chronic obstructive pulmonary disease (COPD), malignancies, and other diseases, and this is the main limitation of its use as a biomarker. Despite this, YKL-40 could be useful in phenotyping when combined with other biomarkers.

Patients with late-onset asthma (LOA) tend to have poor clinical outcomes. Osteopontin (OPN) is a matricellular protein that mediates diverse biological functions and is linked to eosinophilic airway inflammation and remodeling [71]. A study compared serum OPN levels between 131 adult asthma patients, 48 with LOA and 83 with early-onset asthma (EOA) and 226 healthy controls (HCs) [72]. The study found that serum OPN levels were significantly higher in asthma patients compared to HCs, and in LOA patients compared to EOA patients ( $p < 0.05$ ). The authors concluded that aging and exposure to viral infections may induce OPN release, modulating inflammation and contributing to the development of LOA. Despite the investigation of OPN as a biomarker in various diseases, including asthma, and its association with disease severity, its clinical application remains limited due to its lack of specificity. OPN is a diverse protein with a broad range of functions [73].

The endogenously produced cannabinoid oleoylethanolamide (OEA) has immunomodulatory effects by binding to cannabinoid receptors (CB1 and CB2) on immune cells such as eosinophils and monocytes. Recent studies have reported higher serum OEA levels in patients with SA or non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD). Additionally, OEA induces IL-33 secretion in airway epithelial cells (AECs), which increases T2 cytokine levels by activating T2 innate lymphoid cells (ILC2s) and eosinophils, promoting T2 airway inflammation [74]. Notably, surface CB2 receptor expression on eosinophils was significantly higher in patients with EA compared to those with non-EA. Blocking CB2 receptors reduces the release of alarmins and T2 cytokines, as well as the recruitment of eosinophils and ILC2s to the airways. This suggests that serum OEA levels may serve as a novel biomarker for classifying high-T2 asthma, which is associated with ILC2 activation and reduced steroid responsiveness [75].

MicroRNAs (miRNAs) are small non-coding RNA molecules, formed by approximately 18–22 nucleotides, which negatively regulate gene expression at the post-transcriptional level [76]. The abnormal regulation of gene expression by miRNAs has been associated with the development and progression of numerous lung diseases, making miRNAs potential new biomarkers for SA. Approximately 90% of circulating miRNAs form complexes with proteins, and the remaining 10% is secreted in exosomes [77], vesicles conferring miRNAs stability and resistance to degradation by endogenous RNases, characteristics that predispose miRNAs in exosomes to be useful as diagnostic biomarkers, predictors of disease progression, and a helpful tool for decision-making strategies. A study evaluated a group of miRNAs (miR-21, miR-223, and Let-7a) both in serum and in exosomes isolated from the serum of asthma subjects and compared with a group of HCs [78]. Only differences were observed at the exosomal level, and no differences were observed in the serum of the patients. The miRNA expression was dependent on the severity of asthma (severe or mild-to-moderate). Another study analyzed blood serum from 60 subjects (mild asthma, moderate-to-severe, and HC) with a total of 365 miRNAs expressed [79]. Plasma miR-140-5p and miR-107 could be useful as diagnostic biomarkers to distinguish asthma patients from HCs.

For predicting the effect of dupilumab, 17 patients with SA treated with dupilumab were studied [80] (10 responders and 7 non-responders), where serum T2 cytokines were equivalent between responders and non-responders based on decreased ACQ by > 0.5 points. However, the baseline serum IL-18 level was significantly lower in responders than in non-responders (responders,  $194.9 \pm 51.0$  pg/mL; non-responders,  $323.4 \pm 122.7$  pg/mL,  $p = 0.013$ ). The authors concluded that a low baseline serum IL-18 level may be a useful predictor of an unfavourable response to dupilumab in terms of the ACQ-6.

A study identifies that serum levels of lysophosphatidylglycerol (LPG) 18:0 are generally elevated in asthmatics and serve as a biomarker for asthma. LPG 18:0 impairs regulatory T cells (Tregs) function via the NAD<sup>+</sup>/SIRT1/FOXp3 pathway, revealing its potential as a biomarker for asthma.

In low-T2 asthma, although neutrophils are the predominant cells in the airway, their quantification has not been defined as a good biomarker [81]. A study investigated the relationship between myeloperoxidase (MPO) and human neutrophil lipocalin/neutrophil gelatinase-associated lipocalin (HNL/NGAL) with inflammation in the airways [82]. The study included 86 children with asthma and 59 control subjects. The results showed that MPO and HNL/NGAL concentrations in sputum were significantly higher in children with asthma compared to controls. Additionally, these concentrations were positively correlated with each other and with asthma severity. Children with moderate-to-severe persistent asthma had higher levels of MPO and HNL/NGAL compared to those with intermittent and mild persistent asthma. A positive correlation was also found between sputum neutrophil counts and MPO and HNL/NGAL concentrations, as well as with FeNO levels. MPO and HNL/NGAL concentrations in sputum could be a good tool for assessing asthma severity in children. However, another study evaluated the levels of serum MPO as a biomarker for assessing asthma control [83]. The study included 94 asthmatic adult patients and 86 HCs. Asthma severity was assessed using the “Global Initiative for Asthma guidelines”, and participants were divided into three groups: good control ( $n = 22$ ), partial control ( $n = 28$ ), and poor control ( $n = 44$ ). MPO levels were significantly higher in asthmatic patients. However, MPO levels did not significantly differ from asthma control levels but showed significant differences with treatment history. There was a non-

significant negative correlation between MPO levels and spirometry variables. ROC curves revealed sensitivity, specificity, and accuracy for MPO (80.9%, 72.1%, and 84.3%, respectively) in predicting asthma severity. In conclusion, serum MPO levels were significantly higher in asthmatic patients compared to HCs. While MPO levels had a non-significant positive correlation with asthma control levels, they showed a non-significant negative correlation with spirometric results. Finally, another study measured the serum level of MPO and its correlation with respiratory function [84]. The study included 130 patients with asthma and 130 age- and sex-matched HCs. MPO levels were significantly higher in the asthmatic group compared to the control group. Serum MPO levels were positively correlated with asthma severity, all cellular content in bronchoalveolar lavage (BAL), and body mass index (BMI), but inversely correlated with respiratory function. MPO levels were significantly higher in SA compared to non-severe forms. The ROC curve also demonstrated good predictive potential of MPO for asthma diagnosis and its severity. In conclusion, serum MPO levels can be used as a good biomarker for the diagnosis of asthma and its severity. However, results should be interpreted with caution, and MPO should be used alongside a panel of biomarkers until further evidence confirms its role in future studies.

S100 calcium-binding protein A9 (S100A9) has been shown to correlate with neutrophil activation in neutrophilic asthma (NA) by activating Toll-like receptor 4 and increasing IL-8 production [85]. A study found that serum levels of S100A9 were higher in NA patients than in non-NA patients, with a positive correlation between serum S100A9 levels and sputum neutrophil counts ( $r = 0.340$ ,  $p = 0.005$ ) [86]. Asthmatic patients with higher S100A9 levels had lower PC20 methacholine values and a higher prevalence of SA ( $p < 0.05$ ). Higher S100A9 levels were observed in sera, BAL fluid, and lung tissues in the mouse model of NA, but not in other mouse models. These findings suggest that S100A9 is a potential serum biomarker and therapeutic target for the NA phenotype in adult asthmatics.

Olfactomedin 4 (OLFM4) is endogenously expressed in mature neutrophils and gastric, intestinal epithelial cells and the prostate [87]. OLFM4 is involved in innate immunity, inflammation, and carcinogenesis [88]. OLFM4 is a neutrophil-specific granule protein, solely expressed in bone marrow and peripheral blood, but serum could be used to evaluate augmented neutrophilic inflammation in the airway of asthmatic subjects [89]. Therefore, serum OLFM4 levels may be useful as a biomarker for NA.

Over the past two decades, omics approaches, such as genomics [90, 91], transcriptomics [92], epigenomics [93], proteomics [94, 95], metabolomics [96, 97], and microbiomics [98], have emerged as valuable tools for precisely endotyping asthma [99]. Continuous research has demonstrated their effectiveness in distinguishing asthma patients from healthy individuals, increasing our understanding of asthma heterogeneity and pathophysiology. These approaches have also provided insights into the biological mechanisms that may influence treatment responses.

In the U-BIOPRED cohort study, 110 proteins were significantly different, mostly elevated, in SA compared to MMA (mild-to-moderate asthma) and HCs [100]. Ten proteins were elevated in SA versus MMA in both U-BIOPRED and BIOAIR [ $\alpha$ -1-antichymotrypsin, apolipoprotein-E, complement component 9, complement factor I, macrophage inflammatory protein-3, IL-6, sphingomyelin phosphodiesterase 3, TNF receptor superfamily member 11a, transforming growth factor (TGF)- $\beta$ , and glutathione S-transferase]. OCS treatment decreased most proteins, yet differences between SA and MMA remained following adjustment for OCS use. The plasma proteomic panel revealed previously unexplored yet potentially useful type-2-independent biomarkers and validated several proteins with established involvement in the pathophysiology of SA.

A study used lipidomics to profile serum glycerophospholipids in asthmatic patients and controls [101]. The potential as a biomarker for the concentration of LPG 18:0 was assessed as being notably higher in asthmatic patients. These levels correlated with asthma severity and control levels.

Early-life alterations in gut microbiome composition may be involved in asthma pathogenesis and microbial metabolites may also potentially serve as valuable biomarkers in asthma [102].

Five exhaled breath volatile organic compounds (VOCs), benzothiazole, acetophenone, 2-pentyl-furan, methylene chloride, and 2-methyl-butane, predicted early improvement as measured by GETE score, whereas another set of VOCs (2-ethyl-1-hexanol, toluene, 2-pentene, nonanal, and an unidentified compound) predicted a decrease in exacerbations higher than 50% over 12 months [103].

These biomarkers are part of ongoing research and clinical trials aimed at improving the management of SA through more precise and personalized treatment approaches. See Table 3.

**Table 3. New biomarkers for SA**

Biomarker	Description	Clinical relevance
YKL-40	A chitinase-like protein elevated in SA	Associated with airway remodeling and inflammation
Osteopontin (OPN)	A matricellular protein linked to eosinophilic airway inflammation and remodeling	Higher levels of late-onset asthma compared to early-onset asthma
Oleylethanolamide (OEA)	An endocannabinoid with immunomodulatory effects	Induces IL-33 secretion, promoting T2 airway inflammation
MicroRNAs (miRNAs)	Small non-coding RNA molecules, regulates gene expression	Potential biomarkers for SA based on their expression in exosomes
IL-18	A cytokine involved in the immune response	Lower baseline levels may predict a favourable response to dupilumab
LPG 18:0	A glycerophospholipid	Elevated levels in asthmatics, impairs Treg function
Myeloperoxidase (MPO)	An enzyme found in neutrophils	Higher levels of SA, correlated with inflammation
S100A9	A protein associated with neutrophil activation	Higher levels in neutrophilic asthma, correlated with sputum neutrophil counts
Olfactomedin 4 (OLFM4)	A protein expressed in neutrophils	Potential biomarker for neutrophilic asthma

IL-33: interleukin-33; LPG: lysophosphatidylglycerol; S100A9: S100 calcium-binding protein A9; SA: severe asthma; T2: type 2; Treg: regulatory T cell

Despite the identification of several promising biomarkers for SA, there remains a significant gap in identifying relevant biomarkers specific to each phenotype and endotype. Additionally, these biomarkers could prove useful in predicting therapeutic responses and improving clinical outcomes in the long-term management of asthma.

### Do biologics have immunomodulatory effects in SA?

Biologics exert significant immunomodulatory effects in the treatment of SA. These therapies target specific pathways involved in the inflammatory process, modulating the immune response. Some effects are directly related to the drug's mechanism of action and the modulated immunological target, while others are not originally related but contribute to the therapeutic benefits. Here are some key points.

- IL-5 pathway:** Mepolizumab (anti-IL-5 IgG1), reslizumab (anti-IL-5 IgG4), and benralizumab (anti-IL-5Ra IgG1) target IL-5 or its receptor, reducing eosinophil differentiation, survival, and activation [104]. Benralizumab uniquely induces apoptosis of IL-5Ra-expressing cells via antibody-dependent cellular cytotoxicity. These agents effectively lower blood and airway eosinophil counts, mitigating eosinophilic inflammation, a hallmark of SA.
- IgE inhibition:** Omalizumab binds to free IgE, preventing its interaction with mast cells and basophils, thereby reducing mediator release and allergic inflammation. Beyond its primary mechanism, omalizumab decreases high-affinity IgE receptor expression on mast cells, basophils, and dendritic cells (DCs), stabilizes mast cells, increases Tregs, and reduces epithelial-derived cytokines (IL-33, IL-25, and TSLP) and IL-13 levels [105]. Notably, in super-responders, its immunomodulatory effects may persist after discontinuation, although high baseline IgE levels can predict the need for retreatment [106].

3. **IL-4 and IL-13 blockade:** Dupilumab targets IL-4Ra, inhibiting IL-4 and IL-13 signalling, reducing T2 inflammation. Clinical effects include decreased FeNO and serum levels of thymus activation-regulated chemokine (TARC), periostin, eotaxin-3, and total IgE in moderate-to-severe asthma [107–110]. Transient blood eosinophilia with dupilumab has been attributed to impaired tissue migration rather than increased production [108].
4. **TSLP inhibition:** Tezepelumab inhibits TSLP, an epithelial cytokine that can trigger different endotypes of asthma inflammation. TSLP is produced mainly by epithelial cells in response to various stimuli (e.g., viruses, pollutants, and allergens) but is also secreted by eosinophils, mast cells, macrophages, fibroblasts, and ILC2 cells. Multiple immune cells, including progenitor cells, eosinophils, basophils, mast cells, ILC2, DCs, and monocytes/macrophages, express TSLP receptors [111, 112]. By blocking TSLP, tezepelumab suppresses upstream signaling, reducing activation of downstream inflammatory pathways.
5. **AHR:** AHR is a core treatable trait in EA, driven by inflammatory phenotypes and endotypes [113–115]. Airway smooth muscle cells (ASMC) are the main effectors, not only through their contractile properties but also via proinflammatory and immunomodulatory functions, secreting cytokines and chemokines [116–118]. ASMC express receptors for TSLP [119], IL-4/IL-13 [120], and IgE [121], but not IL-5R [122]. Thus, omalizumab, dupilumab, and tezepelumab can modulate AHR directly via ASMC and indirectly via eosinophilic inflammation and neural pathways, whereas mepolizumab and benralizumab reduce AHR predominantly through their anti-eosinophilic effects [115]. Overall, these immunomodulatory effects of biologics lead to reduced exacerbation rates, improved lung function, and enhanced quality of life in patients with SA.

### Could biologics reverse bronchial remodeling?

Airway remodeling is a fundamental feature of asthma, present in both severe and mild forms [123]. It involves structural changes in the large and small airways and lung parenchyma [122, 124], clinically manifesting as airway hyperreactivity and fixed airflow obstruction. Key remodeling features include epithelial barrier damage [125, 126], subepithelial matrix and collagen deposition [127–129], infiltration, cell infiltration and activation [130–132], goblet cell metaplasia [133], inflammatory angiogenesis [134, 135], and airway smooth muscle (ASM) hyperplasia and hypertrophy [136–139]. Subepithelial fibrosis results from fibroblast-to-myofibroblast transition (FMT) induced mainly by TGF- $\beta$  [140]. Table 4 summarizes the changes in remodeling in SA.

**Table 4. Remodeling in SA**

Aspect	Description	Clinical relevance
Epithelial barrier	Damaged epithelial barrier stimulates ECM production by airway epithelial and smooth muscle cells.	Leads to subepithelial fibrosis and reduced airway compliance.
Subepithelial fibrosis	Increased deposition of ECM components, including fragmented and disorganized fibrillar collagen.	Associated with asthma severity and inversely correlated with FEV <sub>1</sub> .
Airway smooth muscle (ASM)	ASM cell hyperplasia and hypertrophy contribute to airway remodeling.	ASM cells have proinflammatory and immunomodulatory functions.
Goblet cell metaplasia	Overexpression of inflammatory angiogenesis and goblet cell metaplasia.	Leads to mucus hyperproduction and airway obstruction.
Angiogenesis	Overexpression of vascular endothelial growth factor and basic fibroblast growth factor.	Contributes to airway remodeling and inflammation.
Inflammatory cells	Persistent airway infiltration/activation of immune cells, including eosinophils.	Contributes to airway alterations and fixed airflow obstruction.
Fibroblast-to-myofibroblast transition (FMT)	Enhanced differentiation of bronchial fibroblasts into myofibroblasts induced by TGF- $\beta$ .	Key aspects of subepithelial fibrosis.

ECM: extracellular matrix; SA: severe asthma; TGF: transforming growth factor

The combination of inflammatory and structural changes in airway remodeling causes the fixed airflow obstruction observed in clinical settings [141]. While biologics primarily target inflammatory pathways in asthma, there is promising evidence that they may also help reverse or reduce bronchial remodeling.

Persistent airway inflammation reduces epithelial barrier integrity, stimulating extracellular matrix (ECM) production by epithelial and ASM cells, promoting collagen and fibronectin deposition by fibroblasts and myofibroblasts [142, 143]. Subepithelial fibrosis results from an imbalance in ECM synthesis and degradation, leading to scarring and reduced airway compliance [144], correlating with disease severity and inversely with FEV<sub>1</sub> [145].

Structural alterations are typically assessed histologically [146], but imaging modalities such as high-resolution CT (HRCT), endobronchial ultrasonography (EBUS), and hyperpolarized gas MRI provide non-invasive evaluation [147]. HRCT has been used to assess treatment response by measuring airway wall thickness [148], airway wall area [149], luminal area [56, 150, 151], and ventilation changes [152]. Studies demonstrate that omalizumab [148], mepolizumab [56, 150], benralizumab [152], and tezepelumab [151] improve structural airway variables, with EBUS showing reduced wall thickening with mepolizumab [153].

Biologic agents reduce eosinophilic and inflammatory cell infiltration, potentially mitigating remodeling [141]. Bronchial biopsies from patients treated with benralizumab and tezepelumab showed decreased eosinophils and ASM mass, though not myofibroblast counts, suggesting effects via depletion of local TGF- $\beta$ 1<sup>+</sup> eosinophils [122].

Clinically, biologics improve airflow obstruction that resists OCS in many SA patients [109, 154–158], with benralizumab [159], mepolizumab [160, 161], omalizumab [162], and dupilumab [108], enhancing lung function and reducing exacerbations, while allowing OCS dose reductions. Tezepelumab rapidly improves FEV<sub>1</sub> by decreasing airway eosinophils and matrix metalloproteinase (MMP)-10 and MMP-3 [163], though OCS-sparing effects remain unproven [164].

Treatment discontinuation studies (e.g., mepolizumab) show lung function deterioration upon stopping, reversed with re-treatment, while some patients maintain improvements post-discontinuation, suggesting lasting anti-inflammatory or anti-remodeling effects [54].

While FEV<sub>1</sub> improvements reflect multiple factors beyond remodeling (e.g., inflammation, AHR, and autonomic modulation) [140], mucus plugs have emerged as key targets. They correlate with goblet cell hyperplasia/metaplasia, galectin-10 activity, ciliated cell dysfunction, and increased MUC5AC/MUC5B expression, leading to airway obstruction [165–168]. Biologics may reduce mucus plugging, contributing to long-term remodeling improvements.

Overall, by modulating eosinophils, mast cells, macrophages, fibroblasts, ASM cells, and cytokine-mediated pathways, biologics can slow or reverse airway remodeling, with efficacy depending on treatment timing and established endpoints.

## Conclusions

Some studies directly or indirectly compare the efficacy of different biological treatments for SA. These studies are essential to determine which treatments may be more effective for various subgroups of patients. The duration of biological treatment for SA depends on several factors, including the patient's response to therapy, the severity of the disease, the control of comorbidities, the use of OCS, and the presence of clinically relevant side effects. The de-escalation of treatment should be gradual and closely monitored. If the patient has achieved remission with biological therapy, reducing or discontinuing biologics should be based on clinical evaluation and biomarkers. Biologics have significant immunomodulatory effects in the treatment of SA. These therapies target specific pathways involved in the inflammatory process, thus modulating the immune response. Emerging biomarkers can help understand the disease's pathophysiology, predict the risk of exacerbations, and tailor personalized treatment strategies. Although biologics primarily target inflammatory pathways in asthma, there is promising evidence that they may also contribute to reversing or reducing bronchial remodeling.

## Abbreviations

ACQ: asthma control questionnaire

ACT: asthma control test

AECs: airway epithelial cells

AERD: aspirin-exacerbated respiratory disease

AHR: airway hyperresponsiveness

ASM: airway smooth muscle

ASMC: airway smooth muscle cells

BAL: bronchoalveolar lavage

BMI: body mass index

COPD: chronic obstructive pulmonary disease

CT: computed tomography

DCs: dendritic cells

EA: eosinophilic asthma

EBUS: endobronchial ultrasonography

ECM: extracellular matrix

EOA: early-onset asthma

FeNO: fractional exhaled nitric oxide

FMT: fibroblast-to-myofibroblast transition

GETE: global evaluation of treatment effectiveness

HCs: healthy controls

HNL/NGAL: human neutrophil lipocalin/neutrophil gelatinase-associated lipocalin

HRCT: high-resolution computed tomography

ICS: inhaled corticosteroids

IL-5: interleukin-5

ILC2s: type 2 innate lymphoid cells

LABAs: long-acting bronchodilator agents

LAMAs: long-acting muscarinic antagonists

LI: leukotriene inhibitor

LOA: late-onset asthma

LPG: lysophosphatidylglycerol

MAIC: matched-adjusted indirect comparisons

miRNAs: microRNAs

MMA: mild-to-moderate asthma

MMP: matrix metalloproteinase

MPO: myeloperoxidase

MRI: magnetic resonance imaging

NA: neutrophilic asthma

NMA: network meta-analysis

NSAID: non-steroidal anti-inflammatory drug

OCS: oral corticosteroids

OEA: oleoylethanolamide

OLFM4: olfactomedin 4

OPN: osteopontin

RCTs: randomized controlled trials

S100A9: S100 calcium-binding protein A9

SA: severe asthma

SGRQ: Saint George's Respiratory Questionnaire

T2: type 2

TARC: thymus activation-regulated chemokine

TGF: transforming growth factor

Tregs: regulatory T cells

TSLP: thymic stromal lymphopoietin

VOCs: volatile organic compounds

## **Declarations**

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DEQ and MM have contributed equally to: Writing—original draft, Writing—review & editing, Conceptualization.

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The authors declare that they have no conflicts of interest.

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