Biological Treatments for Severe Asthma: A Comprehensive Review

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ABSTRACT

Severe asthma is a chronic condition marked by persistent symptoms and frequent exacerbations, often despite high-dose inhaled corticosteroids and other standard therapies. This condition, affecting about 5-10% of asthma patients, significantly contributes to healthcare costs and reduced quality of life. Severe asthma disproportionately impacts certain populations and necessitates systemic corticosteroids, which can cause serious adverse effects. Advances in biologic therapies offer targeted treatments for severe asthma, improving disease management by addressing specific inflammatory pathways. These biologics, such as omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab, and tezepelumab, have shown efficacy in reducing exacerbations, improving asthma control, and reducing corticosteroid dependency. Selection of appropriate biologic therapy depends on clinical characteristics, biomarkers, and comorbidities. The potential for spacing or discontinuing biologic treatments after achieving control is a critical area for future research. These treatments have revolutionized severe asthma management, enhancing patient outcomes and quality of life.

INTRODUCTION

Severe asthma is a long-term respiratory disorder marked by continuous symptoms and frequent flare-ups, even when using high doses of inhaled corticosteroids (ICS) and other conventional treatments. The Global Initiative for Asthma (GINA) guidelines describe severe asthma as a condition necessitating high-dose ICS combined with an additional controller (and/or systemic corticosteroids) to keep it from becoming "uncontrolled," or that remains "uncontrolled" despite such treatment.[1]. The prevalence of severe asthma is approximately 5-10% among asthma patients, contributing significantly to the overall burden of the disease pertaining to of healthcare costs, hospitalizations, and reduced life quality. The economic impact is considerable, with direct medical costs stemming from hospital admissions, emergency department visits, and medication, as well as indirect costs such as lost productivity and absenteeism from work[2-5].

Severe asthma disproportionately affects specific populations, including those with lower socioeconomic status and certain ethnic groups, who may face barriers to accessing specialized care and advanced treatments[4]. Furthermore, the psychological impact on patients and their families is considerable, often resulting in anxiety, depression, and a lower standard of living. The need for systemic corticosteroids, especially oral corticosteroids (OCS), due to frequent flare-ups and poor asthma control, is linked to serious long-term side effects. These side effects include osteoporosis, high blood pressure, diabetes, weight gain, cataracts, and a heightened risk of infections.[6] The urgency to minimize these adverse effects has led to the development of biologic therapies designed to decrease or eliminate the dependence on OCS. The advent of biological treatments has provided new hope for these patients, offering targeted therapies that address specific pathways involved in asthma pathophysiology, thus improving disease management and outcomes.

Pathophysiology of Severe Asthma

Severe asthma is often marked by chronic airway inflammation, airway hyperresponsiveness, and structural changes (remodelling) in the airways. The inflammatory process in severe asthma can be driven by various immune pathways, with type 2 (T2) inflammation being the main one. T2 inflammation is mediated by cytokines such as interleukin (IL)-4, IL-5, and IL-13, which lead to the recruitment and activation of eosinophils, production of IgE, and mucus hypersecretion[3]. These cytokines are produced by T-helper type 2 (Th2) cells any type 2 innate lymphoid cells (ILC2s), contributing to the perpetuation of inflammation and the clinical presentation of asthma[6].

However, not all severe asthma is T2-high; there are also T2-low phenotypes characterized by neutrophilic or paucigranulocytic inflammation[3,5]. These phenotypes are often driven by Th1 or Th17 cells and associated with different inflammatory mediators such as IL-8, IL-17, and tumor necrosis factor-alpha (TNF-α)[7]. The heterogeneity of severe asthma underscores the need for personalized treatment approaches that can effectively target the underlying mechanisms of each phenotype.

Remodelling of the airways in severe asthma includes morphological changes such as epithelial damage, subepithelial fibrosis, smooth muscle hypertrophy, and angiogenesis7-[8]. These alterations lead to the chronic and often irreversible airflow limitation seen in severe asthma patients. Additionally, genetic and environmental factors, including allergens, pollutants, and respiratory infections, play significant roles in the exacerbation and progression of the disease[9].

Biological Treatments

Omalizumab

Mechanism of Action: Omalizumab works as an anti-IgE monoclonal antibody by binding to free IgE, thereby blocking its interaction with high-affinity receptors on mast cells and basophils, which in turn prevents the release of inflammatory mediators. (Table 1)[5].

Eligibility Criteria: Omalizumab is suitable for patients aged 6 and above with moderate-to-severe persistent allergic asthma, who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms remain uncontrolled despite high-intensity treatment.[10].
Predictors of Good Response: Elevated blood eosinophils and high FeNO levels have exhibited a better response to omalizumab[10-11]. Baseline IgE level is not a predictor for good response[12].

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Table 1. Overview of biological treatments for severe asthma

Biologic	Mechanism of action	Dose and Route	Eligibility criteria	Predictors of good response	Main side effects
Omalizumab	Anti-IgE monoclonal antibody	Subcutaneous injection: 150-375 mg every 2-4 weeks	Moderate-to-severe persistent allergic asthma with positive skin test or in vitro reactivity to a perennial aeroallergen, inadequately controlled on ICS	Elevated blood eosinophils, high FeNO, serum periostin	Injection site reactions, anaphylaxis
Mepolizumab	Anti-IL-5 monoclonal antibody	Subcutaneous injection: 100 mg every 4 weeks	Severe eosinophilic asthma identified by blood eosinophil counts	High baseline blood eosinophil counts	Headache, injection site reactions, back pain
Benralizumab	Anti-IL-5 receptor alpha monoclonal antibody	Subcutaneous injection: 30 mg every 4 weeks for first 3 doses, then every 8 weeks	Severe eosinophilic asthma	High baseline blood eosinophil counts	Headache, pharyngitis
Reslizumab	Anti-IL-5 monoclonal antibody	Intravenous infusion: 3 mg/kg every 4 weeks	Severe eosinophilic asthma identified by blood eosinophil counts	High baseline blood eosinophil counts	Oropharyngeal pain, elevated creatine phosphokinase
Dupilumab	Anti-IL-4 receptor alpha monoclonal antibody	Subcutaneous injection: 400-600 mg initially, then 200-300 mg every 2 weeks	Moderate-to-severe asthma with eosinophilic phenotype or OCS-dependent asthma	Elevated blood eosinophils, high FeNO levels	Injection site reactions, conjunctivitis, eosinophilia
Tezepelumab	Anti-TSLP monoclonal antibody	Subcutaneous injection: 210 mg every 4 weeks	Severe uncontrolled asthma	Effective regardless of baseline eosinophil count	Nasopharyngitis, headache

Efficacy:

- Omalizumab remarkably reduces the rate of severe asthma exacerbations by 44% with improvement in quality of life, symptom control and lung function as noted in a meta-analysis of multiple RCTs[13]. On the other hand, there are no RCTs that looked at the OCS-sparing effect. However, in a meta-analysis of observational studies, it has been found that Omalizumab reduced the rate of patients receiving maintenance OCS by 41% while significantly improving their symptom control[14].

Adverse Effects: The most reported adverse effects include injection site reactions and anaphylaxis, which occurs in about 0.1-0.2% of patients[15].

Mepolizumab

Mechanism of Action: Mepolizumab is an anti-IL-5 monoclonal antibody that binds to IL-5, a cytokine crucial for the growth, activation, and survival of eosinophils. By neutralizing IL-5, mepolizumab reduces blood and tissue eosinophils 9 (Table 1)[17].

Eligibility Criteria: Mepolizumab is indicated for patients aged 6 years and older with severe eosinophilic asthma.

Predictors of Good Response: Higher baseline peripheral eosinophil counts predict a better response to mepolizumab compared to sputum eosinophils or FeNO[18].

Efficacy:

- Mepolizumab remarkably reduces exacerbations by around 50% in comparison to placebo. On the other hand, there were statistically significant improvement in SGRQ indicating better quality of life as well as improvement in the ACQ-5 reflecting better asthma control along with lung function Improvement. However, they were less than minimally important clinical difference[19]. The SIRIUS trial addressed the oral corticosteroid-sparing effect of mepolizumab and showed significant sparing effect in patients requiring maintenance oral corticosteroid while maintaining good effect on exacerbation reduction and symptom control[20].

Adverse Effects: Frequent side effects include headache, nasopharyngitis and injection site reactions[20].

Benralizumab

Mechanism of Action: Benralizumab is an anti-IL-5 receptor alpha monoclonal antibody that results in apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC) (Table 1)[5].

Eligibility Criteria: Benralizumab is indicated for patients aged 12 years and older with severe eosinophilic asthma.

Predictors of Good Response: Higher baseline blood eosinophil counts are associated with a better response to benralizumab[21-22].

Efficacy:

- Benralizumab significantly reduces exacerbations and improves pre-bronchodilators FEV1 in patients with baseline eosinophils count of 300 per microliter or higher21-22. Additionally, while reducing exacerbations, Benralizumab has shown profound oral corticosteroids sparing effect noted in the ZONDA trial23. Moreover, Benralizumab significantly enhances asthma symptoms and quality of life24.

Adverse Effects: Frequent side effects include headache and pharyngitis[20].

Reslizumab

Mechanism of Action: Reslizumab is an anti-IL-5 monoclonal antibody which attaches to IL-5, hendring it from interacting with its receptor on

eosinophils, thereby reducing eosinophil levels (Table 1)[5].
Eligibility Criteria: Reslizumab is indicated for patients aged 18 years and older with severe eosinophilic asthma.

Predictors of Good Response: High baseline peripheral eosinophil counts is associated with a better response to reslizumab compared to sputum eosinophils or FeNO[25].

Efficacy:

- *Exacerbation Reduction*: Reslizumab reduces asthma exacerbations by approximately 50% with improvement in asthma control as well as lung function[25-26,]

Adverse Effects: Reported side effects include headache and respiratory infections.[27]

Dupilumab

Mechanism of Action: Dupilumab is an anti-IL-4 receptor alpha monoclonal antibody that blocks the signaling of both IL-4 and IL-13, major cytokines involved in T2 inflammation (Table 1)[5].

Eligibility Criteria: Dupilumab is indicated for patients aged 12 years and older with moderate-to-severe asthma with an eosinophilic phenotype or oral corticosteroid-dependent asthma[28].

Predictors of Good Response: Elevated peripheral eosinophils and elevated FeNO levels are exhibit better response to dupilumab[28-29].

Efficacy:

- Dupilumab significantly reduces exacerbation rates including the ones leading to ER visits and hospitalizations[28]. Moreover, it improves asthma control in addition to prebronchodilator and postbronchodilator FEV1 while exerting notable oral corticosteroid sparing effect[30-31].

Adverse Effects: Common side effects include injection site reactions, conjunctivitis, and asymptomatic hypereosinophilia in most of the cases. However, few cases of eosinophilic granulomatosis with polyangiitis have been reported[28,32-33].

Tezepelumab

Mechanism of Action: Tezepelumab is an anti-thymic stromal lymphopoietin (TSLP) monoclonal antibody that blocks TSLP, an epithelial cytokine that has a key role in initiating allergic inflammation (Table 1)[34].

Eligibility Criteria: Tezepelumab is indicated for patients aged 12 years and older with severe, uncontrolled asthma irrespective of inflammatory phenotype.

Predictors of Good Response: Tezepelumab has shown efficacy regardless of baseline eosinophil count, presenting it as a possible choice for T2-low asthma[35].

Efficacy:

- Tezepelumab notably reduces exacerbation by 56% in patients with eosinophils count of 300 per microliter or higher and by 41% in patients with counts less than 300. Additionally, it enhances asthma control, quality of life as well as lung function[35]. Tezepelumab mitigates the inflammatory biomarkers including blood eosinophils, FeNO as well as IgE and it also reduces the airway hyperresponsiveness as observed by attenuation of mannitol responsiveness[36-37]. While failed to meet the primary endpoint of oral corticosteroid sparing effect in the SOURCE trial, it is likely the design of the trial that led to the negative result [38].

Adverse Effects: Common adverse effects include nasopharyngitis and headache[39].

Safety of Biologics in Pregnancy

The safety of biologic therapies in pregnancy is a crucial consideration for women of childbearing age with severe asthma. Given the potential risks to both the mother and the fetus, it is crucial to assess the safety profiles of these treatments in pregnancy. The safety data regarding the use of biological treatments in pregnancy is very limited, primarily because pregnant women are excluded from clinical trials.

Omalizumab

Omalizumab has been studied in a prospective observational study (EXPECT) involving pregnant women who received at least one dose within 8 weeks before conception or at any point during pregnancy. Despite the small sample size, no increased frequency of major anomalies was observed[40].

Mepolizumab, Benralizumab, and Reslizumab

Given the absence of adequate and well-controlled human studies, these biologics should only be administered during pregnancy if the potential benefits justify the potential risks to the fetus. Clinicians should weigh the severity of the mother's asthma and the potential consequences of uncontrolled asthma against the unknown risks of these treatments during pregnancy. There are ongoing registries for each of these medications to assess the safety of exposure of pregnant women to these medications. However, no results are available yet. Limited case reports showed no adverse outcomes upon use of mepolizumab and benralizumab in pregnancy [41-42].

Dupilumab

Similarly, no adequate studies assessed the safety of dupilumab in pregnancy. The decision to use dupilumab during pregnancy should be decided individually, taking into account the potential benefits and risks. Dupilumab has been found to be safe in a case series of 11 pregnant women who received it as part of management of atopic dermatitis [43].

Tezepelumab

Tezepelumab is a newer biologic with limited data on its use during pregnancy. As a category C drug, its safety profile is not well-established, and it should be used during pregnancy only if the expected benefits outweigh the risks.

Selection of the Biological Treatment

All the currently approved treatments showed excellent clinical outcomes. However, there is no head-to-head clinical trial to prove superiority of one over the other. Therefore, determining the most appropriate biologic therapy for severe asthma requires a thorough evaluation of the patient's clinical attributes, biomarkers, comorbidities, response predictors, and treatment preferences. The following factors should be considered when choosing a biologic:

Phenotype and Biomarkers

Most biologics target T2 inflammation. Patients with elevated blood eosinophils, high FeNO levels, or elevated serum IgE are more likely to benefit from these treatments.

Omalizumab is suitable for patients with allergic asthma and elevated IgE levels. *Mepolizumab, benralizumab and reslizumab* are reserved for patients with eosinophilic asthma. *Dupilumab is* beneficial in patients with both eosinophilic and atopic asthma especially those with high FeNO levels. On the other hand, *tezepelumab is* effective across different phenotypes, including T2-low asthma.

Comorbidities

Consideration of asthma-related comorbidities can alter the choice of biologic therapy:

- *Atopic Dermatitis*: Dupilumab may be preferred due to its efficacy in both asthma and atopic dermatitis [44].
- *Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)*: Dupilumab and mepolizumab have shown benefits and are approved in patients with these comorbid conditions[45-46]. Moreover, omalizumab improves objective and subjective nasal outcomes [47].
- *Hypereoinsophilic syndrome*: Mepolizumab is effective and FDA approved for the management of these comorbidities [48].
- *Eosinophilic granulomtosis with polyangiitis*: Mepolizumab is also approved for the management of this condition. Moreover, Benralizumab has been found recently to be non-inferior to mepolizumab in the management of EGPA [49-50].
- *Urticaria*: omalizumab is approved for its management [51].

Oral corticosteroid dependency

While all biological treatments showed excellent OCS sparing effect, dupilumab is the only biological treatment that is approved for severe OCS dependent asthma irrespective of the inflammatory phenotype.

Spacing or Discontinuation of Biological Treatments

The management of severe asthma with biologic agents has shown remarkable efficacy in reducing exacerbations, improving lung function, and enhancing the quality of life. However, the long-term use of these treatments raises questions about the possibility of spacing (extending the interval between doses) or discontinuation after achieving good control or remission.

Clinical guidelines currently provide limited recommendations on the discontinuation or spacing of biologics. The decision to taper or stop biologic therapy should be individualized, considering factors such as the patient's asthma severity, duration of remission, biomarkers, and history of exacerbations. Studies and real-world data offer some insights into the feasibility and outcomes of such strategies.

Multiple studies were done to investigate the effect of discontinuing omalizumab with conflicting results. The XPORT study investigated the effects of discontinuing omalizumab in patients who had achieved good asthma control[52]. The study found that a significant proportion of patients experienced loss of asthma control or experiencing an exacerbation within 1 year of discontinuation, indicating the need for ongoing treatment in many cases. Another study showed that the effects of omalizumab persisted for 4 years after the discontinuation of treatment[53].

Mepolizumab discontinuation has been looked at in different non-controlled observational studies which revealed worsening of asthma control by increase in the asthma control questionnaire (ACQ) score [54-55]. Moreover, it was studied in a randomized, placebo-controlled, double-blind trial which showed an increase in the rate of significant exacerbations by 14% [56].

Another study that investigated the discontinuation of biological treatments in cases of severe asthma is an observational controlled (propensity score matched wit) study which included 1247 patients who discontinued biological treatments and were compared to similar number of patients who continued on biological treatments. The variables used included age, sex, exacerbation history, comorbidities and income. The biological treatments include omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab. Failure of discontinuation was defined as an increase of 50% or more in the exacerbations that requires treatment with oral corticosteroids and/or lead to health-care utilization. The results revealed no significant difference between the two groups [57].

Tezepelumab is a newer biological treatment and data on the long-term discontinuation of tezepelumab are still emerging.

Patients receiving biological treatments can be classified based on their response into non-responders, partial responders and super-responders [58-60]. The definition of super-responders varies between different reports resulting in variable range of prevalence. Expert agreed that super-responders can be defined by improvement in at least 3 domains evaluated over a year. The major criteria include exacerbation elimination, significant improvement in asthma control, and discontinuation of maintenance oral corticosteroids. Minor criteria include 75% reduction in exacerbation, well control asthma and improvement in FEV1 by at least 500 ml [61].

The results of the discontinuation studies are conflicting but might indicate that a subset of patients especially the super-responders to biological treatments in the discretion of their physicians might be able to space or discontinue their biological treatment[62].

When considering spacing or discontinuation of biologics, regular monitoring of asthma symptoms, lung function, and biomarkers (such as blood eosinophils and FeNO) is essential. A stepwise approach, gradually extending the interval between doses while closely observing the patient's response, may help identify those who can successfully reduce or stop treatment without compromising asthma control.

CONCLUSION

Biologic agents have transformed the management of severe asthma, offering targeted treatment options that significantly reduce exacerbations, improve asthma control and lung function, and decrease the need for oral corticosteroids. Each biologic has distinct mechanisms of action, eligibility criteria, and predictors of good response, allowing for personalized treatment approaches. Continued research and head-to-head trials will further refine and optimize the use of these life-changing treatments. Additionally, the potential for spacing or discontinuation of biologic treatments after achieving good control remains an important area for future studies, with the goal of minimizing medication burden while maintaining optimal asthma management.

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