Targeted Therapy for Severe Asthma: Identifying the Right Patients

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Abstract Asthma affects over 300 million people worldwide. Most asthmatics are well controlled with inhaled corticosteroids and long-acting beta-agonists; however, a proportion of patients are unresponsive and attain limited disease control. This group represents a considerable healthcare and financial burden, particularly patients who experience frequent exacerbations and require hospital admission. Development of new biological agents and disease biomarkers has provided novel avenues for treatment. These treatments have been highly successful, reducing exacerbations and yielding modest improvements in quality of life and lung function. However, only a proportion of severe asthmatics respond to this targeted treatment, highlighting the heterogeneity of severe asthma. One of the first biological therapies targeted immunoglobulin E (IgE) and demonstrated modest benefit but could only be used in a subgroup of patients. Recent research has shown that treatment aimed at the T helper-2-(Th2)-high pathways and cytokines such as interleukin (IL)-5, IL-4, and IL-13 may also be effective in another partially overlapping subgroup. A blood eosinophil count over a defined threshold (generally ≥300 cells/μl) was a reliable biomarker and identified the majority of responders in this group. Further discovery and validation of biological markers to define asthmatic phenotypes that may benefit from biological treatments remain an area of intense interest and research. We review the latest information pertaining to biological agents and demonstrate how patient responders may potentially be identified for treatment.

Key Points

Severe asthmatics uncontrolled with standard treatment with long-acting beta-agonist and inhaled corticosteroids may be eligible for and responsive to biological therapies that target cytokines.

Phenotyping severe asthmatics using a combination of biomarkers may be the best way to identify which patients are likely to derive benefits from targeted anti-cytokine therapy.

A blood eosinophil level of ≥300 cells/μl is currently the most easily accessible biomarker to identify severe asthmatics who are likely to respond to biological therapies that target cytokines.

1 Introduction

Asthma affects over 300 million people worldwide and is estimated to cause 1/150 deaths worldwide [1]. Severe asthma accounts for approximately 10–15% of the asthmatic population, but it may utilize up to 50% of overall healthcare costs for asthma [2, 3]. Severe asthma not only imposes a significant burden on the healthcare system but also affects individuals and their families, leading to additional financial and emotional burdens [2–4].

The majority of asthmatics can be adequately controlled with inhaled corticosteroids (ICS) and long-acting beta-
agonist (LABA) treatments; however, despite correct use of these medications, approximately 10% of asthmatics still have uncontrolled severe disease [2] as defined by European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines [5]. Considerable heterogeneity exists within the severe asthma group, and the importance of elucidating the different phenotypes of asthma that may benefit from personalized treatments has been emphasized [6]. Specifically, reliable biomarkers that aid in the selection of patients who may benefit from targeted treatments remain the focus of current research.

Interventions that target cytokine activities in asthma have generated considerable interest following successful clinical trials of omalizumab, mepolizumab, and, most recently, reslizumab and benralizumab [7–14]. However, clinical and spirometry improvements were noted in only in a proportion of severe asthmatics, chiefly those with an eosinophilic phenotype. This highlighted the need to carefully select appropriate patients for treatment and emphasized the necessity of reliable biomarkers with which to identify responders.

This review discusses new compounds targeting cytokines and the role of biomarkers in the identification of responder patients, with a focus on clinically accessible biomarkers, and examines projected developments in the field.

2 What is Severe Asthma?

Modern targeted treatments are directed at severe asthma unresponsive to optimized current management. In this context, the accurate diagnosis of severe disease is paramount. Severe asthma is defined by the recent ERS/ATS guidelines as “asthma which 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.” In patients with severe asthma, by this definition, uncontrolled asthma is then defined by at least one of the following: (1) poor symptom control (Asthma Control Questionnaire [ACQ] >1.5 or Asthma Control Test [ACT] <20); (2) frequent severe exacerbations (two or more bursts of systemic corticosteroids in the previous year); (3) serious exacerbations (at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year); and (4) airflow limitation (forced expiratory volume in 1 s [FEV\(_1\)] <80% predicted) [5]. Additionally, severe asthma can only be diagnosed after appropriate treatment of comorbidities and exclusion of other conditions that may mimic asthma [5, 15]. However, once this severe group has been identified, further interventions are merited, and this has driven development of recent innovative approaches based on an enhanced understanding of disease pathways in severe asthma.

3 How Better Understanding of Asthma Pathologies Facilitated Targeted Therapies for Severe Asthma

The underlying pathogenesis of allergic asthma can be broadly characterized as T helper-2 (Th\(_2\)) cell-mediated disease. Cytokines generated from Th\(_2\) cells, including interleukin (IL)-4, IL-5, and IL-13, are now known to be closely associated with pathogenetic mechanisms in asthma [16–20]. During this complex process, interactions between environmental factors and host immune and inflammatory responses are postulated to lead to production of Th\(_2\)-type cytokines (see Fig. 1) such as IL-4, IL-5, and IL-13 that may be amenable to intervention. Type 2 innate lymphoid cells (ILC2s) are also important cells involved in eosinophilic asthma-like airway inflammation and produce type 2 cytokines, similar to Th\(_2\) cells, including IL-4, IL-5, IL-9, and IL-13. ILC2s can be activated by airway epithelium-producing cytokines such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) [21].

Key actions of IL-4 include shifting Th\(_0\) cells to differentiate into Th\(_2\) cells and an immunoglobulin class switch that induces immunoglobulin E (IgE) production from B cells [19, 20]. IgE binds to the high-affinity IgE receptor (F\(\varepsilon\)RI) on mast cells and basophils, and antigen crosslinking of IgE leads to degranulation and release of inflammatory mediators, including histamine, prostaglandins, and pro-inflammatory cytokines (IL-4, IL-5, IL-13) [16–20, 22]. In the lower airways, this activity may result in eosinophilia, increased mucus production, and enhanced smooth muscle contractility [20, 23].

IL-5 is a key cytokine for eosinophil growth, differentiation, recruitment, activation, and survival [24–29]. The cytokine also works in conjunction with IL-9 to recruit mast cells and eosinophils to affected tissue sites [30, 31]. In animal models, IL-5 gene disruption leads to eosinopenia and blocking of allergen-induced airway eosinophilia [32]. Although IL-5 has a key role in severe disease, anti-IL-5 strategies in unselected asthma groups initially had disappointing clinical outcomes [33]. IL-13 is closely linked to IL-4 since both cytokines signal through heterodimeric IL-4R\(\alpha\)/IL-13R\(\alpha\) receptors [34]. Blocking IL-4R\(\alpha\) therefore blocks the effects of both IL-4 and IL-13. IL-13 causes goblet cell hyperplasia, mucus production, and airway hyper-responsiveness and can also mediate isotype switching of activated B cells to produce IgE [34–36].
Patients with ‘Th2-high’ asthma typically have eosinophilic inflammation mediated by cytokines IL-4, IL-5, and IL-13 and may have raised IgE. Conversely, ‘Th2-low’ asthma is characterized mainly by neutrophilic inflammation and in some cases is paucigranulocytic [37–40]. IL-8 is also increased in airways of non-eosinophilic asthma [40]. Woodruff et al. [17] demonstrated that Th2-low asthmatics (and healthy controls) also expressed IL-5 and IL-13 but at lower levels than eosinophilic asthmatics. IL-4 levels were similar between Th2-high and Th2-low groups [17]. IL-8 was increased in airways of non-eosinophilic asthmatics [40]. There are currently no biomarkers to identify Th2-low asthma, but the disease process may involve Th17 and Th1 cells. Th17 cells are cluster of differentiation (CD)-4 + T cells that produce a number of cytokines, including IL-17A, 17E, IL-17F, and IL-22 [16, 41–44]. IL-17A and IL-17F stimulate airway cells to secrete neutrophil chemoattractants such as CXCL8 (IL-8) that mediate neutrophil infiltration and increased airway inflammation [44]. Th1 cells also produce tumor necrosis factor (TNF)-α, an important mediator of severe asthma since it induces airway inflammation, hyper-responsiveness, mucous hyper-secretion, and macrophage activation [16]. It is therefore important to appreciate that a significant (approximately 30–50%) proportion of severe asthmatics do not have Th2-high disease [39, 45, 46]. The limitations of exclusively targeting IL-5 and similar cytokines are obvious and emphasize the need for accurate biomarkers to identify responders.

4 Biomarkers of T-Helper-2 Cell (TH2) Inflammation

As outlined, eosinophils are a fundamental component (and marker) of asthma pathophysiology in many severe asthmatics. Methods to detect eosinophilic airway inflammation are thus important to help identify patients who may benefit from biological therapies targeting Th2 cytokines (see Table 1).
4.1 Sputum Eosinophils

Sputum eosinophilia ≥3% has been widely used in clinical studies as a biomarker for eosinophilic airway inflammation [9, 47–50]. A landmark study in moderate to severe asthmatics used sputum eosinophil counts as a basis on which to adjust ICS. Treatment strategies to normalize sputum eosinophilia reduced asthma exacerbations and admissions without the need for additional anti-inflammatory treatment [49].

The value of sputum eosinophil counts was highlighted in the recent ERS/ATS guidelines that recommended using sputum eosinophil counts in combination with clinical criteria to guide asthma therapy [5]. Unfortunately, sputum eosinophil analysis outside research settings has proved to be difficult to implement. Limitations include that not all asthmatics are able to produce sputum, the analysis of sputum for eosinophilia requires specially trained laboratory staff, and the test is labor-intensive, limiting widespread use of this biomarker [51].

4.2 Peripheral Blood Eosinophils

Peripheral blood eosinophil counts are easy to obtain and have been demonstrated to be relatively closely related to sputum eosinophil counts [52, 53]. A prospective study by Wagener et al. [52] examined 110 patients with mild to moderate asthma and found that blood eosinophil count had the highest concordance with eosinophilia (defined as sputum eosinophils ≥3%). A peripheral blood eosinophil count of \(0.27 \times 10^9/l\) had sensitivity of 78% and specificity of 91% in distinguishing eosinophilic versus non-eosinophilic airway inflammation. These and other studies have shown that blood eosinophil counts are a reliable way to identify sputum eosinophilia (and superior to fraction of exhaled nitric oxide [FeNO] and periostin) [53].

Measuring blood eosinophils may have other benefits. For example, in a prospective study of >1000 asthmatics, an absolute peripheral blood eosinophil count of >0.45 \(\times 10^9/l\) was associated with a sevenfold increase in the relative risk of asthma-related death [54]. A cohort study of over 12,000 asthmatics found that blood eosinophil counts >0.3 \(\times 10^9/l\) were associated with asthma-related emergency department visits [55].

However, the most accurate cut point for blood eosinophilia to predict clinical responses to biological treatments is still to be determined. Various studies have used different cut points [14, 50, 56], and it seems likely that individual thresholds may vary depending on the specific monoclonal antibody used for treatment.

It is also important to remember that there is significant diurnal viability in blood eosinophil counts [57]. Some studies made allowance for variability and included patients who had raised eosinophils in the year prior to recruitment [8, 10].

4.3 Other Biomarkers of Th2 Inflammation

4.3.1 Fraction of Exhaled Nitric Oxide (FeNO)

Nitric oxide is generated from the lung airway epithelium and is present in exhaled breath [58, 59]. It is measured as FeNO and is recommended by the ATS/ERS guidelines as an important adjunct in the management of severe asthma [5].

In patients with well-controlled asthma, the upper limit of normal for FeNO is 25 ppb. FeNO >50 ppb in adults may reflect airway inflammation and may signify airway eosinophilia, and responsiveness to ICS is likely in symptomatic patients. Patients with persistently elevated FeNO, especially if adherent to corticosteroid treatment, may thus have corticosteroid-unresponsive asthma [59]. However, a Cochrane meta-analysis reported insufficient evidence to monitor corticosteroid therapy with FeNO alone [60] and suggested that the measurement should be used as one component of integrated clinical asthma management. A limitation is that this recommendation was based on studies not evaluating patients with severe asthma.

4.3.2 Immunoglobulin E (IgE)

IgE is a key downstream biomarker of Th2 inflammation. Westerhof et al. [61] reviewed 336 adults with asthma and looked at the diagnostic accuracy of total IgE, blood eosinophils, and FeNO for predicting sputum eosinophilia (defined as ≥3%). At a specificity of ≥95%, sensitivities for FeNO, blood eosinophils and combined did not significantly differ, but the sensitivity of IgE was significantly lower. Conversely, at a sensitivity of ≥95%, FeNO, blood eosinophils, and IgE had comparable specificity. However, IgE was less predictive of sputum eosinophilia in atopic and obese patients [61].

4.3.3 Periostin

Periostin expression is elevated in the bronchial epithelial cells of a subset of asthmatics. When stimulated by IL-13, these epithelial cells secrete periostin into the extracellular matrix, with accumulation in the peripheral blood [62]. The protein has been tried as a biomarker for lebrikizumab responsiveness. Treatment improved FEV1 compared with placebo in patients with increased periostin, but improvements in patients with low periostin were minimal. These early studies indicated that periostin may aid identification of IL-13-dependent Th2 inflammation and act as a biomarker for effective anti-IL-13-based therapies [63].
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<td>+++</td>
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\(^a\) Adis
should be remembered that periostin is secreted by osteoblasts as part of bone abnormalities (e.g., bone metastasis, fractures, osteoporosis), potentially making periostin levels difficult to interpret [62].

5 Monoclonal Antibody Therapies Targeting TH2 Based on the Use of Biomarkers

5.1 Anti-Interleukin (IL)-5 Therapies Using an Eosinophil Biomarker

Anti-IL-5-based therapies target the IL-5-signaling pathway and have been widely researched. These monoclonal antibodies can exert their effect by blocking either the endogenous IL-5 ligand (mepolizumab, reslizumab) or the IL-5 receptor (benralizumab).

5.1.1 Mepolizumab

Mepolizumab is a humanized monoclonal antibody, immunoglobulin G1 (IgG1) that targets IL-5 with high affinity and specificity. It blocks binding of human IL-5 to the α chain of the IL-5 receptor located on the eosinophil cell surface. This action inhibits IL-5 signaling followed by reduced production and survival of eosinophils. Mepolizumab has been approved by the Therapeutic Goods Administration (TGA) in Australia, European Medicines Agency (EMA), and the US FDA as add-on treatment for severe refractory eosinophilic asthma in patients aged ≥12 years. Mepolizumab is approved only for subcutaneous use [24].

Considerable research has been performed in mepolizumab, and initial clinical trials in unselected asthmatics were disappointing [25, 33]. However, in follow-up studies, asthmatics with eosinophilic airway inflammation responded to mepolizumab, yielding reduced asthma exacerbations [8, 47] and reductions in oral corticosteroid use [9, 10].

The DREAM study was a large multicenter study that evaluated different doses of mepolizumab (intravenous 75, 25, 750 mg, or placebo) in asthma. Eosinophilic airway inflammation was defined as blood eosinophils ≥300 cells/µl or ≤< 300 cells/µl.

Biomarker Targeted therapy Outcomes studied Selection criteria/biomarker cut-offs Value

| Unselected | Reslizumab [67] | Change in FEV₁ | No biomarker cut-off used in selection criteria |
| Unselected for Th₂ inflammation | Baseline blood eosinophils <400 cells/µl | 0 |
| | Baseline blood eosinophils ≥400 cells/µl | +++ |
| Tralokinumab [77] | Exacerbations | No biomarker used in selection criteria |
| Non Th₂ therapy | | Biomarkers not employed |

Table 1

| Unselected | Reslizumab [67] | Change in FEV₁ | No biomarker cut-off used in selection criteria |
| Unselected for Th₂ inflammation | Baseline blood eosinophils <400 cells/µl | 0 |
| | Baseline blood eosinophils ≥400 cells/µl | +++ |
| Tralokinumab [77] | Exacerbations | No biomarker used in selection criteria |
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| Tralokinumab [77] | Exacerbations | No biomarker used in selection criteria |
| Non Th₂ therapy | | Biomarkers not employed |

IIgE immunoglobulin E, IL interleukin, FEV₁ forced expiratory volume in 1 s, FeNO fraction of exhaled nitric oxide, ELEN index eosinophil/lymphocyte and eosinophil/neutrophil index (the ELEN index is a mathematical algorithm to predict elevated sputum eosinophils ≥2%)

a 0 indicates no value (biomarker not useful in predicting response to therapy); + indicates limited value (biomarker has only limited reliability in predicting response to treatment); ++ indicates moderate value (biomarker can be used with moderate confidence in predicting response to treatment); +++ indicates significant value (biomarker can be used with high confidence in predicting response to therapy)

b Optimization phase was designed to establish the lowest dose of maintenance oral glucocorticoids associated with acceptable asthma control

c Patients were then stratified at randomization (2:1) according to baseline blood eosinophils ≥300 cells/µl or <300 cells/µl

d Dupilumab improved exacerbations and FEV₁ irrespective of baseline eosinophil levels

e Subgroups for post hoc analysis: low blood eosinophil (<260 cells/µl) and high blood eosinophil (≥260 cells/µl); low FeNO (<24 ppb) and high FeNO (≥24 ppb); low serum periostin (<50 ng/ml) and high serum periostin (≥50 ng/ml)

f High Th₂ (IgE >100 IU/ml and blood eosinophil count ≥0.14 × 10⁹ cells/l) and low Th₂ groups (IgE ≤ 100 IU/ml or blood eosinophil <0.14 × 10⁹ cells/l)
pathway [64, 65]. The EMA and FDA approved it in March 2016 as add-on maintenance therapy via intravenous administration in severe asthmatics aged ≥18 years with an eosinophilic phenotype.

Reslizumab improved multiple measures of asthma control in patients with inadequately controlled asthma and blood eosinophils ≥400 cells/μl. Castro et al. [12] conducted two replicate phase III trials [12]. In both studies, patients receiving reslizumab had a significant reduction in asthma exacerbations compared with placebo. Pooled data also demonstrated significantly improved FEV₁, Asthma Quality of Life Questionnaire (AQLQ) scores and ACQ-7 scores. Importantly, this is one of the few studies that demonstrated a reduction in the use of corticosteroids, with sub-analysis showing the cumulative rescue systemic corticosteroid burden was greater in the placebo group (611 mg/patient) than in the reslizumab group (254 mg/patient) [66].

In a phase III study, Bjørmer et al. [13] studied the effect of intravenous reslizumab at two different dose levels (0.3 and 3 mg/kg) in patients with persistent inadequately controlled asthma and elevated blood eosinophils (≥400 cells/μl). The primary endpoint was change in FEV₁, FEV₁ at 16 weeks improved significantly with reslizumab 0.3 mg/kg (115 ml; p = 0.02) and 3.0 mg/kg (160 ml; p = 0.001) compared with placebo [13]. Both doses of reslizumab improved rescue inhaler use, ACQ score, and asthma symptoms. Although results are promising, whether this translates to reductions in exacerbations or corticosteroid use remains to be seen. Most frequent adverse events were worsening of asthma, nasopharyngitis, and headache. Anaphylaxis was rare [12, 13].

Finally, Corren et al. [67] conducted a phase III trial to evaluate the efficacy of reslizumab in asthmatics. The difference in this trial was that it also recruited those with blood eosinophil levels <400 cells/μl. There was no significant improvement in the primary endpoint of FEV₁ compared with placebo in the subgroup with baseline eosinophils <400 cells/μl. However, sub-analysis in patients with ≥400 cells/μl did show benefit, with improvement in FEV₁ and ACQ-7 compared with placebo [67].

5.1.3 Benralizumab

Benralizumab is a humanized monoclonal antibody directed against the α chain of the IL-5 receptor (anti-IL-5RαIgG1) on eosinophils and basophils. Blocking the IL-5-IL-5Rα interaction induces apoptosis of eosinophils and basophils by antibody-dependent cell-mediated cytotoxicity, thereby depleting blood and airway eosinophils [68–70].

Several studies have been reported in severe asthma. In a randomized controlled double-blind dose-ranging phase IIb trial, uncontrolled asthmatics treated with ICS and LABA received benralizumab or placebo. This was one of the first studies to use an indirect measure of sputum eosinophilia by defining an eosinophilic phenotype as Eosinophil/Lymphocyte and Eosinophil/Neutrophil (ELEN) index positive or FENO ≥5 ppb. The ELEN index is a mathematical algorithm to predict elevated sputum eosinophils >2%. Exacerbation rates did not significantly differ in the treatment groups (doses of 2 mg or 20 mg; p = 0.781 and p = 0.173). Post hoc analyses showed that patients who received any dose of benralizumab and had blood eosinophils ≥300 cells/μl had significant improvements in ACQ-6 scores and FEV₁ [14].

Bleecker et al. [71] conducted a recently published phase III trial (SIROCCO) in patients with severe asthma that was uncontrolled with high-dose ICS and LABA. Participants received benralizumab 30 mg every 4 weeks or every 8 weeks or placebo. Patients were stratified at baseline into high blood eosinophil (≥300 cells/μl) or low blood eosinophil (<300 cells/μl) groups. In asthmatics with eosinophil counts ≥300 cells/μl, benralizumab reduced asthma exacerbations by 51% and improved FEV₁ by approximately 150 ml (pre-bronchodilator). Adverse events were mild and included nasopharyngitis, upper respiratory infection, and worsening of asthma [71]. A similar trial by FitzGerald et al. [72] reported comparable results.

5.2 Anti-IL-13-Based Therapies Using Eosinophils and Periostin Biomarkers

IL-13 and IL-4 are closely linked since both bind to the heterodimeric combination of the α1 chain of the IL-13 receptor (IL-13Rα2) and the α chain of the IL-4 receptor (IL-4Rα1). Targeting IL-4Rα with an antibody aimed at this receptor blocks the downstream effects of both IL-4 and IL-13 [34].

5.2.1 Lebrikizumab

Lebrikizumab is an IgG4 humanized monoclonal antibody that blocks the binding of IL-13 to IL-4Rα and therefore blocks IL-13 activity [73]. Initial studies were disappointing in unselected asthmatics [74]. However, by selecting asthmatics based on biomarkers, a sub-group of asthmatics was identified who may benefit. The biomarker was periostin, an index of IL-13 activation [63].

In a phase II study (MILLY), Corren et al. [63] studied adult asthmatics with inadequately controlled asthma despite ICS. Participants received subcutaneous lebrikizumab once a month for 6 months or placebo. Approximately 80% of patients were also receiving LABA. Patients were initially stratified according to Th2 status, with high
Th2 defined as total IgE >100 IU/μl or eosinophil count >0.14 × 10⁹ cells/l. Analyses were later changed to assess outcomes based on periostin levels since the assay became available after study commencement. The lebrikizumab group showed improvement in pre-bronchodilator FEV₁ and was most improved in the high-periostin subgroup. However, this improvement in FEV₁ did not translate to clinical improvement; lebrikizumab had no significant effect on ACQ-5 scores or rate of exacerbations [63].

In a phase II trial (MOLLY), uncontrolled asthmatics not treated with ICS received lebrikizumab or placebo. No improvement in FEV₁ was noted despite stratification into periostin subgroups [75]. The lack of response in this group of asthmatics highlights the importance of ICS. It also suggests that the need for ICS therapy may be a proxy measure for other as yet undefined patient characteristics that determined responses to lebrikizumab in other studies.

More recently, Hanania et al. [56] conducted phase IIB trials and analyzed lebrikizumab in patients with moderate-to-severe asthma in two randomized placebo-controlled studies (LUTE and VERSE). Uncontrolled asthmatics receiving ICS and a second controller were enrolled, and analysis was based on high serum periostin levels (≥50 ng/ml) or low serum periostin levels (<50 ng/ml). Periostin-high patients experienced a 60% reduction in rate of exacerbations. Periostin-low patients experienced only a 5% reduction in exacerbations. Raised FeNO (≥21 ppb) and blood eosinophils (≥240 cells/μl) were both predictive of treatment response. Although lebrikizumab improved exacerbation rates, there were no clinically significant improvements in asthma symptoms or quality of life [56].

Two recently released phase III studies (LAVOLTA I and LAVOLTA II) evaluated uncontrolled asthmatics receiving ICS and a second controller medication. Biomarker-high patients (serum periostin ≥50 ng/ml or blood eosinophils ≥300 cells/μl) had reductions in exacerbation rates [76].

5.2.2 Tralokinumab

Tralokinumab is an anti-IL-13 monoclonal antibody that neutralizes IL-13 but does not affect the activity of IL-4 [77]. Brightling et al. [77] conducted a phase IIB study with tralokinumab in patients with severe uncontrolled asthma who were treated with high-dose ICS and LABA. Overall, tralokinumab did not significantly reduce asthma exacerbation rates. Patients receiving tralokinumab every 2 or 4 weeks exhibited a significant increase in FEV₁ compared with placebo. ACQ-6 and AQLQ scores did not differ, and analysis of the high-periostin subgroup showed non-significant reductions in all parameters. A potential biomarker identified in this study, dipetidyl peptidase-4 (DPP-4), is the product of a gene that is induced by IL-13 in healthy and asthmatic airway epithelial cells. It will be used to stratify patients in subsequent studies with tralokinumab [77].

5.3 Anti-IL-4 and IL-13 Therapies Using an Eosinophilic Biomarker

5.3.1 Dupilumab

Dupilumab is a fully human monoclonal antibody to the α subunit of the IL-4 receptor that inhibits both IL-4 and IL-13 signaling [48]. Wenzel et al. [48] conducted a phase II study evaluating subcutaneous dupilumab 300 mg weekly for 12 weeks or placebo in patients with persistent moderate-to-severe asthma and elevated blood eosinophil counts (≥300 cells/μl or sputum eosinophil count ≥3%). During the study, LABA and then ICS were withdrawn. Exacerbation rates were reduced by 87% in the dupilumab group. There were also improvements in FEV₁ and ACQ-5 score [48].

Subsequently, a phase Iib dose-ranging trial with dupilumab in patients with uncontrolled persistent asthma receiving medium- to high-dose ICS and LABA, irrespective of baseline eosinophil counts, was conducted. Patients received subcutaneous dupilumab 200 mg or 300 mg every 2 or 4 weeks or placebo over 24 weeks. Dupilumab administered every 2 weeks decreased severe asthma exacerbations and improved FEV₁. For the overall population, severe exacerbation risk reduction was ~70%. The main adverse events reported were upper respiratory tract infection, injection-site erythema, and headache [78]. This study was the first pivotal study to show efficacy with anti-IL-4/IL-13 therapy, and phase III studies are currently underway.

5.4 Anti-IgE Therapy Using IgE as Biomarker

Biological anti-IgE treatments have been used for over a decade, and a very brief overview is presented. Omalizumab is a humanized monoclonal antibody that works by reducing serum IgE levels. It binds to the Cε3 domain of IgE secreted by activated B cells and prevents interaction with the high-affinity FcεRI receptor on mast cells, eosinophils, basophils, and dendritic cells [79]. Omalizumab is approved for use as add-on therapy in inadequately controlled severe persistent allergic IgE-mediated asthma that requires continuous or frequent treatment with oral corticosteroids [20].

A Cochrane review in 2014 examined 25 trials and found that omalizumab was effective in reducing asthma exacerbations in moderate or severe asthma. When omalizumab was used in patients with moderate or severe asthma receiving ICS therapy, asthma exacerbations

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reduced (odds ratio [OR] 0.55). The omalizumab group also exhibited a reduction in hospitalizations, and patients were more likely to be able to reduce or withdraw ICS [20].

Hanania et al. [80] studied patients with uncontrolled severe asthma who were treated with placebo or omalizumab in the prospective multicenter randomized parallel-group double-blind placebo-controlled EXTRA study. Patients were divided into low- and high-biomarker subgroups. Biomarkers including FeNO, blood eosinophils, and serum periostin were evaluated to predict the effectiveness of omalizumab. The cut-offs used to define high- and low-biomarker groups were as follows: low- and high FeNO subgroups (<24 ppb; ≥24 ppb); low and high blood eosinophils (<260 cells/µl; ≥260 cells/µl), and low and high serum periostin (<50 ng/ml; ≥50 ng/ml). Despite some limitations (incomplete biomarker data), they found that patients with three positive high biomarkers at baseline had a greater reduction in exacerbations after 48 weeks of omalizumab. IgE serum levels have not been particularly useful as a biomarker to predict response to omalizumab [80].

5.5 Monoclonal Antibody Therapies Targeting Non-Th2 Asthma Without Biomarker Use

Brodalumab is a human anti-IL-17RA immunoglobulin G2 (IgG2) monoclonal antibody that binds with high affinity to IL-17RA and blocks the biological activity of IL-17A, IL-17F, IL-17A/F heterodimer, and IL-25 [42]. A study was conducted using brodalumab in moderate-to-severe asthmatics receiving regular ICS, and results showed improvements in ACQ scores, FEV₁, and symptom-free days [42].

TNF-α receptor blockers such as etanercept [82] and golimumab [82] have not shown any clinical benefit in asthma. Holgate et al. [81] performed a phase II randomized controlled trial of etanercept in moderate-to-severe asthmatics receiving high-dose ICS. Although etanercept was well tolerated, there were no improvements in FEV₁ (primary endpoint) or ACQ-5 scores (secondary endpoints) [81]. Golimumab was studied in patients with uncontrolled persistent asthma receiving high-dose ICS and LABA but yielded no improvement in FEV₁ or exacerbation rates. Risk of malignancy and serious infection was increased with golimumab, and studies were subsequently ceased [82].

6 Why Do Targeted Therapies Fail?

Targeting the pathways involved in Th2 inflammation in asthma has been successful, and eosinophils appear to be a reliable biomarker to detect patients in whom this strategy may be effective. However, a significant number of severe asthmatics (approximately 30–50%) do not have a Th2-high phenotype, which will limit the use of these new therapies [39, 45, 46]. The Belgian Severe Asthma Registry showed that raised blood eosinophil counts of >220 cells/µl (0.22 × 10⁹/l) were only present in 53% of patients, and sputum eosinophilia >2% was only detected in 55% of severe asthma. The remaining asthmatics had neutrophilic or paucigranulocytic cell profiles, representing a group in whom Th2-based treatments may not work [39].

Other factors may prevent or attenuate responses. In severe disease, airway remodeling occurs and may lead to fixed airway narrowing, limiting symptomatic responses and improvements in FEV₁ [83–85]. Inflammatory processes may differ in asthma depending on the stage of disease [6, 85]. This in turn may blunt the effect of targeted therapies that may only work where Th2 inflammation is active. Acute or chronic endobronchial infection may alter Th2 profiles and reduce responses. Finally, vocal cord dysfunction and other co-morbidities such as reflux can also make asthma seemingly difficult to treat and need to be excluded as a cause of or an exacerbating factor for severe asthma [5].

7 Future Directions

Considerable research has been put into phenotyping severe asthma to enable personalization of therapies [86–88]. Most recently, the SARP-3 (Severe Asthma Research Program-3) explored the clinical and inflammatory characteristics of exacerbation-prone asthmatics. Biomarkers used to measure type 2 inflammation, including blood eosinophils, sputum eosinophils, FeNO, and IgE, did not aid detection of asthmatics at frequent risk of exacerbations [87]. The U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Diseases Outcome Consortium) is an asthma biomarker study that aims to enable personalization of therapies [89]. The most recent update from U-BIOPRED in mild–moderate and severe asthmatics found four phenotypes (see Table 2). A key limitation was that not all patients were able to produce a sputum sample, and therefore sputum proteomics data were available in only 86 of 318 participants [88].

Asthma metabolomics studies have been used to find novel biomarkers. Metabolomics is the study of small molecules, including carbohydrates, amino acids, organic acids, and lipids [90, 91]. Exhaled breath condensate, urine, and blood metabolomics profiles have been used to try and discriminate different asthma phenotypes. However, whether these metabolomics-based biomarkers can be translated into clinically useful biomarkers is the focus of ongoing research [91].
Future prospects for non-eosinophilic (neutrophilic) asthma include macrolide antibiotic therapy. Clarithromycin used in severe asthmatics reduced sputum neutrophilia and IL-8 and improved quality of life but did not affect FEV$_1$ [92]. The AZISAST (Azithromycin for prevention of severe asthma trial) [93] post hoc analysis found that azithromycin led to a reduction in severe exacerbations in non-eosinophilic asthmatics (defined as a blood eosinophil count $\leq$200 cells/μl) compared with placebo.

Finally, bronchial thermoplasty involves bronchoscopy where the large airways are heated using radiofrequency energy, resulting in a reduction in airway smooth muscle [94]. A large sham-controlled trial found that bronchial thermoplasty reduced severe asthma exacerbations and improved asthma-specific quality-of-life scores. The number of adverse events was high (8.4% of those receiving bronchial thermoplasty required hospitalization vs. 2.8% of patients in the sham group). One patient was hospitalized due to hemoptysis requiring bronchial artery embolization.

8 Conclusion

The benefits of new biological agents to treat severe asthma clearly depend on the selection of an appropriate patient population. Clinical studies have shown that a biomarker identifying a specific subgroup (high blood eosinophilis) works well in a clinical context. Although other biomarkers have been researched, blood eosinophil counts appear to be most useful.

However, a large proportion of severe asthmatics have $\text{Th}_2$-low or no discernable $\text{Th}_2$ inflammation. More innovation is needed to develop new therapies and expand the repertoire of biomarkers to identify severe asthma phenotypes likely to respond to targeted treatments.

Compliance with Ethical Standards

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