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REVIEW

Severe refractory asthma: current treatment options and ongoing research

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Abstract

Patients with severe asthma have a greater risk of asthma-related symptoms, morbidities, and exacerbations. Moreover, healthcare costs of patients with severe refractory asthma are at least 80% higher than those with stable asthma, mainly because of a higher use of healthcare resources and chronic side effects of oral corticosteroids (OCS). The advent of new promising biologicals provides a unique therapeutic option that could achieve asthma control without OCS. However, the increasing number of available molecules poses a new challenge: the identification and selection of the most appropriate treatment. Thanks to a better understanding of the basic mechanisms of the disease and the use of predictive biomarkers, especially regarding the Th2-high endotype, it is now easier than before to tailor therapy and guide clinicians toward the most suitable therapeutic choice, thus reducing the number of uncontrolled patients and therapeutic failures. In this review, we will discuss the different biological options available for the treatment of severe refractory asthma, their mechanism of action, and the overlapping aspects of their usage in clinical practice. The availability of new molecules, specific for different molecular targets, is a key topic, especially when considering that the same targets are sometimes part of the same phenotype. The aim of this review is to help clarify these doubts, which may facilitate the clinical decision-making process and the achievement of the best possible outcomes.

Keywords: cytokines, economic burden, endotypes, eosinophils, inflammation, phenotypes.

Citation


Introduction

Patients with severe asthma have an increased risk of asthma-related symptoms, morbidities, and exacerbations.1-2 Moreover, healthcare costs of patients with severe refractory asthma are at least 80% higher than those with stable asthma because of a higher use of resources.3,4 Approximately, up to 30% of patients with refractory asthma still require regular use of oral corticosteroids (OCS).5 Prolonged use of OCS may lead to several side effects such as osteoporosis, fracture, infections, obesity, symptomatic coronary artery disease, avascular necrosis, stroke, cataract, glucose metabolism changes, and skin thinning.6 In addition, there is an obvious concern about the adverse effects, especially growth, induced by OCS in children.7 The potential side effects of OCS heavily affect patients’ quality of life and sustain a big economical burden.

The advent of new promising biological therapies provides a strategy to avoid OCS damage and to improve global asthma control. For several years, the only available biologic therapy has been omalizumab, a monoclonal antibody (mAb) that targets immunoglobulin E (IgE) and is used for a specific subpopulation of patients with uncontrolled IgE-mediated allergic asthma. Recently, new drugs and nonpharmacologic options, such as anti-interleukin (IL)-5 mAbs, anti-IL-4/IL-13, and bronchial thermoplasty, are available as upcoming options, supported by encouraging results for patients not eligible or not responsive to omalizumab (Table 1). Due to the number of available treatment alternatives, the identification of the right drug for the right patient represents a key aspect of treatment, which can be implemented by new biomarkers reflecting an underlying disease mechanism, in addition to the correct use of those already available.
In this review, the management of available therapies and the overlapping aspects of some of those treatments as well as their application in clinical practice will be discussed. The future availability of new molecules that are specific for different targets is a key topic, especially when considering that the same targets are sometimes part of the same phenotype. It is important to address and clarify some of these aspects, which may further facilitate the clinical decision-making process to identify the most successful treatment option and obtain the best possible outcomes.

**Methods**

For this review, a search strategy based on validated keyword filters was devised to select articles regarding severe asthma and its management. In detail, a selective search on medical databases (in particular PubMed and Medline) was carried out up to February 2018, and research papers, international guidelines, recommendations, position papers, systematic reviews, and Cochrane meta-analyses relevant to the topic have been considered. The search strategy was based on the following keywords: inflammation, asthma phenotypes, asthma endotypes, T2-low and T2-high subtypes, IgE, eosinophils, cytokines, IL-5, IL-4, IL-13, and costs. A total of 245 potential papers were identified in the first search through databases, and 115 of these were considered eligible. Only original studies with human subjects were considered, and only full texts were included among those potentially relevant. Case reports and purely descriptive studies were excluded.

### Severe asthma treatments: Th2 versus non-Th2

Asthma is recognized as a complex condition with differences in severity, natural history, comorbidities, and treatment response. A longstanding debate in the asthma field is whether asthma is a single disease with a variable presentation, or several diseases that have variable airflow obstruction as a common feature. Therefore, different definitions have been proposed based on the ‘observable characteristics’ – the phenotypes – which describe clinical, physiological, morphologic, and biochemical characteristics as well as the response to different treatments. However, even if clinically relevant, phenotypes do not provide any insight on the underlying disease mechanism. Thus, in relation to asthma heterogeneity, the term ‘endotype’ has recently been introduced to describe a subtype of a condition defined by a unique or distinctive functional or pathophysiologic mechanism.

Currently available treatments and most of the upcoming ones are directed to the inflammatory Th2 endotype that drives the inflammation in about 50% of asthma patients. The mechanisms underlying the dysregulation of innate and adaptive Th2 immunity in severe asthma have been intensively analyzed in a recent review. Cytokines, chemokines, and mediators involved in the Th2-signaling and inflammatory response are targets of new biologic therapies for severe asthma.

### Table 1. Biodrug options for severe asthma.

<table>
<thead>
<tr>
<th>Drug (Administration)</th>
<th>Regimen</th>
<th>Target population</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-IgE</strong> (Subcutaneous)</td>
<td>From 75 mg up to 1200 mg every 2/4 weeks</td>
<td>Early onset asthma. Serum total IgE levels 30 ≤ IgE ≤ 1500 IU/mL, Positive skin prick test or specific serum IgE for perennial allergens</td>
<td>Confirmed long-term efficacy both in adults and in children, antiviral effect, prevention of seasonal exacerbations</td>
</tr>
<tr>
<td><strong>Anti-IL-5</strong></td>
<td>100 mg every 4 weeks</td>
<td>Eosinophilic asthma ≥300 cells/µL, NP – CSWNP(^5), late onset asthma</td>
<td>Excellent safety profile, demonstrated clinical effect, and steroid-sparing effect</td>
</tr>
<tr>
<td><strong>Anti-IL-13</strong></td>
<td>30 mg every 4 weeks for the first 3 doses, then every 8 weeks</td>
<td>Eosinophilic asthma ≥300 cells/µL, NP – CSWNP(^5), late onset asthma</td>
<td>High affinity for IL-5 receptor and ADCC activity, eosinophils total tissue depletion, improvement of pulmonary function</td>
</tr>
<tr>
<td><strong>Reslizumab</strong> (Intravenous)</td>
<td>3 mg kg(^{-1}) every 4 weeks</td>
<td>Eosinophilic asthma ≥300 cells/µL, NP – CSWNP(^1)</td>
<td>Personalized dosage and improvement of pulmonary function</td>
</tr>
<tr>
<td><strong>Anti-IL-4/ IL-13</strong> (Subcutaneous)</td>
<td>300 mg every 4 weeks</td>
<td>Eosinophilic asthma ≥150–300 cells/µL, aspirin-exacerbated respiratory disease (AERD)(^*)</td>
<td>Significant steroid-sparing effect and improvement of pulmonary function</td>
</tr>
</tbody>
</table>

\(^*\)Aspirin-exacerbated respiratory disease (AERD): defined by a physician diagnosis of asthma, chronic rhinosinusitis with nasal polyposis, and a convincing clinical history of nonsteroidal anti-inflammatory drug (NSAID) sensitivity. \(^5\)CSwNP, chronic sinusitis with nasal polyposis; NP, nasal polyposis. ADCC, antibody-mediated cell cytotoxicity; IgE, immunoglobulin E; IL, interleukin.
Moreover, recent data are increasingly confirming the role of Th17 cells and IL-17: neutralization of IL-4 and/or IL-13 resulted in increased Th17 cells and neutrophilic inflammation in the lung, which confirms that Th2 and Th17 inflammatory pathways are reciprocally pathways are almost all targeted by the available mAbs and other mediators will be targeted in the next future (Table 2).12

Regarding the neutrophilic non-Th2 endotype, currently there are not effective therapeutic options, even if some chemo-attractant antagonists for neutrophils have shown promising results in early human trials.13 Moreover, recent data are increasingly confirming the role of Th17 cells and IL-17: neutralization of IL-4 and/or IL-13 resulted in increased Th17 cells and neutrophilic inflammation in the lung, which confirms that Th2 and Th17 inflammatory pathways are reciprocally

Table 2. Non-Th2 and Th2 strategies under investigation.

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Target</th>
<th>Therapy</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th2</td>
<td>IgE</td>
<td>Omalizumab</td>
<td>Available</td>
</tr>
<tr>
<td></td>
<td>IL-5</td>
<td>Mepolizumab</td>
<td></td>
</tr>
<tr>
<td>Th2</td>
<td>IL-5</td>
<td>Reslizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-5Ra</td>
<td>Benralizumab</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td>IL-13Rβ</td>
<td>Lebrikizumab</td>
<td>investigation</td>
</tr>
<tr>
<td></td>
<td>IL-4α</td>
<td>Dupilumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-13</td>
<td>Tralokinumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GATA3</td>
<td>GATA3 DNAzyme</td>
<td></td>
</tr>
<tr>
<td>Non-Th2</td>
<td>Airways smooth muscle</td>
<td>Bronchial thermoplasty</td>
<td>Available</td>
</tr>
<tr>
<td></td>
<td>TSLP</td>
<td>Tezepelumab</td>
<td>Under investigation</td>
</tr>
<tr>
<td></td>
<td>PDG2 antagonist</td>
<td>Fevipiprant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ILC2</td>
<td>Anti-CRTH2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>Anti-CXCR2</td>
<td></td>
</tr>
</tbody>
</table>

CRTH2, chemoattractant receptor-homologous molecules expressed on Th2 cells; CXCR2, CXC chemokine receptor 2; IgE, immunoglobulin E; IL, interleukin; ILC2, type II innate lymphoid cells; PDG2, prostaglandin D2; Th, T helper 2; TSLP, thymic stromal lymphopoietin.

Figure 1. Inflammatory pathway in asthma.

Neutrophils activation

Eosinophils activation

IFNγ, interferon gamma; IL, interleukin; ILC2, type II innate lymphoid cells; TH, T helper; TSLP, thymic stromal lymphopoietin.
regulated in asthma (Figure 1). Other studies have highlighted the role of Group 2 innate lymphoid cells (ILC2s) in asthma pathogenesis and regulation of inflammation.\(^\text{14}\) This enormous progress in understanding the inflammatory pathways could pave the way to the development of non-Th2 endotype target drugs in the next future (Table 2).

**Anti-IgE approach**

In IgE-mediated asthma, allergens exposure, IgE antibodies, and their binding to high-affinity (FceRI) and low-affinity (FceRII or CD23) receptors on the surface of effector cells (mast cells and basophils) induce degranulation and release of cytokines and inflammatory mediators, which leads to the bronchoconstriction associated with asthma exacerbations.\(^\text{15}\)

Omalizumab is a murine mAb that has been used in clinical practice since 2003 for the treatment of severe allergic refractory asthma in patients with serum IgE levels ranging between 30 and 1500 IU/mL. This mAb is the result of a somatic cell hybridization method and is able to bind to FcεRI and FcεRII receptors of basophils, dendritic cells, and mast cells.\(^\text{16}\)

In the past decade, studies have confirmed the efficacy and safety of omalizumab, in terms of significant reduction in the frequency of asthma exacerbations (up to 50%), quality of life (QoL) improvement, and a significant steroid-sparing effect.\(^\text{17}\)

This mAb showed a good efficacy profile even in non-allergic asthma,\(^\text{18}\) which can be explained by the possible existence of a local IgE production without systemic sensitization.\(^\text{19}\)

Recent studies have confirmed its effectiveness in pediatric patients with refractory asthma,\(^\text{20}\) mainly in the prevention of seasonal exacerbations, thanks to the ability of omalizumab to restore interferon-α response to rhinoviruses.\(^\text{21}\)

According to the available evidence, omalizumab treatment should be continued without suspension, as the IgE levels and the number of FcεRI receptors increase 3–4 weeks after its suspension, resulting in a worsening of asthma control, especially in patients with higher levels of eosinophilia, periiostin, and fractional exhaled nitric oxide (FeNO).\(^\text{22}\)

In fact, the presence of these biomarkers seems to be related to a better response to omalizumab, but also to a more rapid loss of its effect after suspension, as shown in XPORT and EXTRA studies.\(^\text{23,24}\)

The prevention of exacerbations by omalizumab was greater in the presence of higher eosinophilic levels, which represents an overlapping aspect between anti-IgE and anti-IL-5 mAbs. In a recent pooled analysis from two pivotal phase 3 trials, the authors found a better omalizumab response in patients with peripheral blood eosinophils levels ≥300 cells/µL.\(^\text{25}\)

In this subgroup, the treatment with omalizumab reduced exacerbations by 67% versus a 45% reduction of exacerbations in patients with values <300 cells/µL. However, greater disease severity, history of emergency asthma treatment, hospitalization, forced expiratory volume in 1 second (FEV\(_1\)), % predicted, inhaled corticosteroids (ICS) dose, and long-acting beta-agonists (LABA) use, were associated with a greater reduction in exacerbation by omalizumab. These data suggested that the preventive benefit may have been more related to disease severity, rather than to blood eosinophilia.

A very recent retrospective real-life study conducted in France on 872 adult and pediatric patients with severe allergic asthma (STELLAIR) has come to different conclusions.\(^\text{26}\)

In this study, the response rate was calculated according to blood eosinophil count measured in the year prior to omalizumab treatment start. According to clinical evaluation, 67.2% of adults and 77.2% of minors were responders, while 71.1% of adults and 78.5% of minors had a >40% reduction in the exacerbation rate. In adults, the response rate for combined criteria was 58.4% for blood eosinophils ≥300 cells/µL and 58.1% for blood eosinophils <300 cells/µL. These data suggested that omalizumab response is unrelated to the level of blood eosinophilia, and therefore this biomarker should not be taken into consideration when choosing omalizumab as a treatment option.

Therefore, the correct selection of the patient for omalizumab implies not only a favorable response in the short term, but also an increase of clinical efficacy in the long term (up to 9 years of follow-up),\(^\text{27}\) with a possible favorable cost-effectiveness profile in patients with refractory asthma, if correctly selected.\(^\text{28}\)

**Anti-IL-5, anti-eosinophils, and the possible overlap with anti-IgE**

Mepolizumab was the first biologic available for severe eosinophilic asthma. It is a humanized non-glycosylated IgG1 antibody blocking IL-5 and preventing the binding of IL-5 to its receptor. The first studies investigated the application of mepolizumab in diseases other than asthma, such as idiopathic hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis (EGPA),\(^\text{29}\) and demonstrated a significant reduction in the use of OCS and a better control of the disease. The dose of mepolizumab in EGPA is 300 mg instead of 100 mg for asthma. Early studies on asthma failed to reach the expected outcomes, as mepolizumab was ineffective in terms of improvement of respiratory function parameters (bronchial hyperresponsiveness, FEV\(_1\), peak expiratory flow – PEF) and reduction of exacerbation.\(^\text{30,31}\)

However, several studies underlined the presence of a bias in patients’ recruitment, as they had not been properly stratified and selected according to their blood eosinophils and asthma severity. Subsequently, the DREAM, MENSA, and SIRIUS registriative randomized clinical trials (RCTs) showed the ability of this drug to significantly improve the control of asthma with a significant steroid-sparing effect in patients with severe asthma with blood eosinophils ≥300 cells/µL.\(^\text{22–24}\)

The MUSCA trial has confirmed that mepolizumab significantly improved the health-related QoL with an early improvement of pre-bronchodilator FEV\(_1\) values sustained up to week 24.\(^\text{35}\)

A post hoc analysis of DREAM and MENSA RCTs showed that baseline blood eosinophil count represents a biomarker predictive of mepolizumab clinical efficacy.\(^\text{36}\) The authors
highlighted clinically relevant reductions in exacerbation rate in patients with a count of 150 cells/µL or more at baseline. Notably, this biomarker, although not specific, could lead to better patients’ selection, especially for those who are likely to achieve important clinical improvement with mepolizumab. In addition, the drug demonstrated an excellent safety profile and a long-lasting and stable effect, as highlighted by the COSMOS study. Another anti-IL-5 is reslizumab, a humanized IgG4k mAb with high affinity for IL-5. This mAb addresses patients with uncontrolled eosinophilic asthma and blood eosinophil level >400 cells/µL, showing a meaningful reduction of sputum eosinophil count, improvement in QoL, FEV1, and reduction of exacerbation rate.\(^{38,39}\)

A post hoc analysis of two identical pivotal trials (Studies 3082 and 3083) showed that patients with asthma, chronic sinusitis with nasal polyposis (CSwNP), and higher blood eosinophila level (400 cells/µL) treated with reslizumab had 83% reduction of the annual rate of exacerbations compared to an overall reduction of 54%.\(^{40}\) These data confirm a major clinical benefit of anti-IL-5 treatment in patients with higher eosinophilia levels and CSwNP. In an open-label extension trial, 1051 patients received intravenous (IV) 3.0 mg/kg reslizumab up to 2 years, with a good safety profile and sustained long-term efficacy in terms of lung function improvements and asthma control.\(^{41}\) These results reinforce the evidence of long-term safety and efficacy in anti-IL-5 mAbs.

A practical limitation of this drug may be the IV administration route, as it implies the availability of a venous access, and the infusion over 20–50 minutes. Currently, the above-mentioned administration route and dosage are the only ones approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA). However, recent data showed that a weight-adjusted dosage represents a potential added value, especially in overweight or obese patients. One study compared the response to weight-adjusted IV reslizumab in 10 prednisone-dependent patients with asthma who were previously treated with 100 mg mepolizumab subcutaneous (SC).\(^{42}\) Reslizumab was shown to further reduce airway eosinophila compared to mepolizumab SC, with a concomitant improvement in asthma control. Two ongoing phase 3 RCTs are evaluating the efficacy of reslizumab SC (ClinicalTrials.gov identifier: NCT02452190 and NCT02501629) and a phase 2–3 study is investigating the monthly infusion of 3 mg/kg IV reslizumab for 4 months in patients with prednisone-dependent eosinophilic asthma previously treated with another IL-5 antagonist (mepolizumab) administered subcutaneously (ClinicalTrials.gov identifier: NCT02559791).

Benralizumab is a IgA1 mAb that binds the epitope on the α-subunit of the IL-5 receptor. It reduces blood eosinophils and their precursors through a completely different mechanism compared to other IL-5 antagonists, based on the induction of antibody-mediated cell cytotoxicity (ADCC).\(^{43,44}\) The constant region (Fc) of benralizumab is afucosylated, leading to a higher affinity for the Fc-gamma III (FcyRlIla) receptor on the surface of mast cells, basophils, and natural killer cells. Through the last, it induces ADCC on eosinophils and basophils.\(^{45}\) The result is an almost complete depletion of eosinophils in sputum and tissues (90% and 96%, respectively), as well as a total depletion in the bone marrow and in the blood.\(^{46}\) In phase 1 and 2 randomized controlled trials, including patients with severe and peripheral eosinophilic asthma (eosinophils > 300 cells/µL), SC benralizumab showed excellent results, especially in terms of reducing inflammatory mediators, as well as causing a significant reduction of blood eosinophils.\(^{47–49}\) Furthermore, different from other anti-IL-5 treatments, benralizumab is independent of circulating IL-5 levels, which tend to increase during asthma exacerbations. The drug is also insensitive to the effect of other cytokines such as IL-3 and GM-CSF, due to the profound depletion of eosinophils.\(^{44}\) All these findings have led to highly promising results in terms of reduction of exacerbations and average dose of OCS, with a response already evident after a single dose. The drug is administered every 4 weeks for the first three doses, then every 8 weeks thereafter.\(^{50}\)

Data from the ZONDA trial substudy showed a tissue depletion of eosinophils induced by benralizumab greater than other anti-IL-5.\(^{51}\) In addition, the effect of benralizumab-based ADCC could overcome the problem of the immune complex formation between mepolizumab and IL-5, which may serve as an IL-5 reservoir and thus determine a partial response to treatment (underdosage), as reported by some researchers.\(^{52}\) The effect of benralizumab on the improvement of FEV1, is evident, even in patients with fixed airflow obstruction (FAO) and obesity, as highlighted by the post hoc analysis of the studies SIROCCO and CALIMA.\(^{53,54}\) Even if at different levels, a few studies have provided evidence of the benefit of the mAbs on the steroid-sparing effect, as evidenced when comparing the data from the ZONDA\(^{55}\) and SIRIUS\(^{56}\) RCTs on benralizumab and mepolizumab, respectively. The former showed that the two benralizumab dosing regimens (30 mg administered subcutaneously either every 4 weeks or every 8 weeks – with the first three doses administered every 4 weeks) significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group (p<0.001 for both comparisons). On the other hand, the latter showed that the median percentage reduction from baseline in the glucocorticoid dose was 50% in the mepolizumab group (100 mg administered SC every 4 weeks for 20 weeks), as compared with no reduction in the placebo group (p=0.007). Even if direct comparative studies are needed, this may suggest a greater effectiveness of benralizumab as compared to the direct competitor.

Moreover, the pre-filled syringe and the administration every 8 weeks reinforce the drug profile in terms of compliance and usability. In accordance with these findings and on the clinical evidence, the baseline factors that positively impact on response to benralizumab are a higher dose of OCS, frequent asthma exacerbations, nasal polyposis, and forced vital capacity (FVC) <65% predicted.\(^{55}\) The sustained tissue
depletion of eosinophils induced by benralizumab may raise some concerns regarding the theoretical risk of tumors, infections, and autoimmune diseases. However, several data have confirmed that the absence of eosinophils from mammals is not associated with any pathology. The observation that eosinophil-deficient mice do not show any characteristic syndrome or global health issues strongly supports that under usual laboratory conditions eosinophil does not play a critical role in maintaining mammalian well-being. On the opposite side, the neutrophils deficiency is typically associated with more frequent bacterial infections. The available data suggest that current anti-eosinophil therapies are safe, although long-term studies are needed to confirm their safety.

The possibility of overlapping target population between omalizumab and anti-IL-5, shown in up to 37% of cases, is a critical topic (Figure 2). It is therefore essential to understand the responder profile of each of the two options, and to identify the potential candidates to a treatment switch, although in the absence of head-to-head comparative studies up to now. Meta-analysis data show that the efficacy of omalizumab and mepolizumab is similar in terms of clinical outcomes. Unfortunately, the heterogeneity of selection criteria and the absence of biomarkers specifically predictive of treatment response make the treatment choice a difficult task.

A post hoc analysis aiming to evaluate the effect of mepolizumab in patients with severe eosinophilic asthma previously treated with omalizumab showed how high levels of IgE and the presence of atopy does not reduce the effectiveness of anti-IL-5. Patients with severe eosinophilic asthma responded positively to mepolizumab regardless of the prior use of omalizumab, thus supporting the switch between anti-IgE and anti-IL-5, in case of ineffectiveness of the former, as a potentially effective intervention.

### Blocking IL-4 and IL-13: role of dupilumab

IL-4 and IL-13 are pleiotropic Th2 cytokines, which share a common receptor, IL-4Rα, and a common pathway. Dupilumab is a new mAb that inhibits the pro-inflammatory effect of these two cytokines through its interaction with the IL-4 α subunit of the IL-4 receptor. Recent studies investigating dupilumab administered SC at doses ranging from 100 to 300 mg showed a significant decrease in the rate of exacerbations, an improvement of asthmatic symptoms and pulmonary function. A reduction of the inflammatory biomarkers related to the activity of Th2 lymphocytes (TARC levels, eotaxin-3, FeNO) without modifications in the eosinophils count (±300 cells/μL) was also noticed. A very recent phase 3 RCT (liberty asthma venture) demonstrated that the greatest efficacy of dupilumab was observed in patients with type 2 profile (blood eosinophil count at baseline ≥150 per cells/μL and baseline FeNO ≥ 25 ppb). Among patients with a blood eosinophil count of >300 cells/μL, treatment with dupilumab
resulted in a 65.8% reduction of the severe exacerbation rate compared to the placebo group.\textsuperscript{65} In another study (liberty asthma quest), the reduction of glucocorticoids was 70.1% in the dupilumab group, compared to 41.9% in the placebo group. Treatment with this mAb resulted in a 59% reduction in severe exacerbation rate with an increase in FEV\textsubscript{1}, of 0.22 L.\textsuperscript{66} It is very important to note that in this study patients were recruited regardless to the presence of type 2 biomarkers, such as baseline blood or sputum eosinophil count, FeNO or IgE. These aspects confirm the great potential of dupilumab not only in Th2 high pattern, but also in neglected phenotypes.

However, some concerns about safety have been raised. An increase in the blood eosinophil count up to >3000 cells/μL was reported in 13% of the patients,\textsuperscript{64} including anecdotal reports of eosinophilic pneumonia. Type 2 cytokines such as IL-4 and IL-13 have been shown to prime migratory responses of the hematopoietic progenitor cells (HPC). Consequently, the increase of blood eosinophilia could be explained by the blocking of the IL4 and IL13 receptor with loss of lung-homing of eosinophils.\textsuperscript{67} Moreover, as Th2 cytokines are powerful suppressors of IL-17 driven-inflammation, Th2-targeted treatment may lead to the amplification of the activity of the opposite Th17 pathway, limiting therapeutic efficacy over time.\textsuperscript{68} Large-scale studies are needed to clarify long-term safety issues. Recently, the United States Food and Drug Administration (FDA) approved dupilumab for groups of uncontrolled asthma patients, those with eosinophilic moderate-to-severe asthma phenotype, even those with oral corticosteroid-dependent asthma, regardless of phenotype (https://www.accessdata.fda.gov/scripts/cder/daf).

### Ongoing research: failures, promises, and unmet needs

Ligelizumab (QGE031), a new anti-IgE mAb, showed at the first phases of its development higher suppression of free IgE when compared to omalizumab; the same effect was observed also in patients with very high IgE levels.\textsuperscript{69} Despite promising initial data, the phase 2 study QGE031B2201 did not satisfy the primary outcome, as the superiority of QGE031 compared to placebo (Novartis Pharmaceuticals, unpublished data) was not demonstrated.\textsuperscript{70} Nevertheless, according to another double-blind RCT parallel groups results, ligelizumab was more effective than omalizumab in terms of skin test positivity suppression and lung function response, demonstrating its potentiality beyond omalizumab.\textsuperscript{71} However, the development of ligelizumab has been currently suspended.

Type 2 immunity is regulated by several transcription factors, such as GATA-3, STAT-6, NFAT, IRF-4, and c-maf. GATA-3 is one of the six members of the GATA transcription factors family and represents the main regulator in Th2 differentiation.\textsuperscript{72} It has been shown to play a key role in mediating the asthmatic immune response, by promoting the production of IL-4, IL-5, and IL-13.\textsuperscript{73} Induction of GATA-3 overexpression in T and ILC2 lymphocytes in experimental models leads to an increased allergic airway inflammation.\textsuperscript{74} It has also been shown that at least part of the corticosteroid therapeutic activity in the treatment of type 2 inflammation can be attributed to an inhibitory effect on the phosphorylation of GATA-3, which suppresses nuclear translocation of this transcription factor.\textsuperscript{75,76} Recent options targeting GATA-3 belong to the new class of antisense oligonucleotide therapeutics, the 10–23 DNA (deoxyribonucleic acid)zymes (DNAzymes) antisense oligonucleotide, which includes SB010.\textsuperscript{77} By cleaving GATA-3 mRNA, SB010 reduces specific cytokine production and thereby exerts its effect on key features of allergic airway inflammation.\textsuperscript{78} Based on the overall positive results of the application of GATA-3 DNAzymes in animal models, phase 1 and 2 RCTs were recently performed with inhaled SB010 in patients with uncontrolled allergic asthma and sputum eosinophilia. SB010 demonstrated a significant reduction of Th2-dependent biomarkers such as sputum eosinophilia, serum IL-5, and tryptase levels.\textsuperscript{79} Further clinical trials are needed in order to confirm the clinical efficacy of this promising molecule.

Prostaglandin D2 (PGD2) is a prostanoid produced primarily by mastcells in atopic subjects. It exerts a pro-inflammatory effect and induces vasodilatation and increased permeability. Fevipirant (QAW039) is a PGD2 antagonist of the chemo-attractant receptor-homologous molecule expressed on Th2 cells (CRTH2). The drug, which can bind receptors on the surface of eosinophils, basophils, and T lymphocytes in the blood and tissues, inhibits the migration and activation of these cells in the airway tissues and blocks the PGD2-driven release of the Th2 cytokines.\textsuperscript{80} RCTs of phase 2 and 3 have been performed in patients with refractory allergic asthma, and others are in progress. Preliminary data confirm a good safety profile, an improvement in asthma control and FEV\textsubscript{1}, especially in patients with more severe obstruction.\textsuperscript{79}

Lebrikizumab (MILR1444A) is a humanized mAb targeting IL-13. In the phase 2 studies, lebrikizumab showed an improvement in pulmonary function and in the control of severe refractory asthma, only in the subgroup of patients with allergic phenotype, including high levels of serum perioستin and exhaled FeNO.\textsuperscript{80} Subsequently, two parallel phase 3 RCTs were conducted to evaluate the effectiveness and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and II). LAVOLTA I met its primary endpoint, showing a significant reduction of asthma exacerbations rate in people with higher levels of serum periostin or blood eosinophils. This study also showed a significant improvement in lung function. Unfortunately, LAVOLTA II study did not confirm the same results.\textsuperscript{81}

Tralokinumab is another anti-IL-13 mAb, whose development is hampered by the poorly encouraging data emerging from two randomized phase 2b trials. In fact, tralokinumab did not show any significant reduction in exacerbations or improve the Asthma Control Questionnaire (ACQ) score.\textsuperscript{82} A post hoc analysis showed a greater improvement in FEV\textsubscript{1}, in the group
with higher basal IL-13 levels (10 μg/mL), suggesting that the presence of residual IL-13 was associated with a higher response in FEV._83 Optimistically, it is possible that a more proper patient selection could improve the drug performance; the same issue limited, at the beginning, mepolizumab efficacy when administered to asthmatic patients independently of their phenotype. Three other randomized phase 2 and 3 RCTs (MESOS, STRATOS 1 and 2) have confirmed the ineffectiveness of tralokinumab in asthma, speculating that the role of IL-13 may not be crucial for the control of eosinophilic airway inflammation._84 In a recent study, adult patients with mild-to-moderate asthma not receiving inhaled corticosteroids (ICS) therapy were randomized to receive lebrikizumab 125 mg SC, placebo SC or montelukast 10 mg orally for 12 weeks._85 Unfortunately, lebrikizumab did not significantly improve the FEV1, probably because the inhibition of IL-13 only did not result in an effective modulation of bronchial inflammation.

Regarding neutrophilic and paucigranulocytic asthma, the treatment options are extremely limited in the field of biologics, as different molecules failed in achieving the primary outcomes. CXCR2-chemokine receptor, a potent chemo-attractant that mediates neutrophil migration in the airways, represents a target currently under investigation. A preliminary study showed a reduction in ruputum and blood neutrophils and a better asthma control based on ACQ, but no significant change in FEV₁ was observed in patients with severe asthma treated with SCH527123, a CXCR2 antagonist._13 Further studies assessed the safety and efficacy of AZD5069, another CXCR2 antagonist, as add-on therapy in patients with severe-uncontrolled asthma._86 Treatment with this CXCR2-selective antagonist did not reduce the frequency of severe exacerbations, thus raising major doubts about the role of CXCR2-mediated neutrophil recruitment in severe refractory asthma exacerbations and potential clinical benefits.

Recently, stem cell factors and its receptors, including the tyrosine kinase inhibitor (KIT), were recently evaluated because of their critical role to mast cell homeostasis. Mast cells are long-living, tissue-dwelling, hematopoietic effector cells that are implicated in the pathobiologic basis of asthma and are present in patients with severe asthma, in face of glucocorticoid therapy. Their presence correlates with airway hyper-responsiveness and asthma severity._87 Imatinib, a KIT inhibitor, showed promising results in a RCT, which reported decreasing airway hyperresponsiveness, mast-cell counts, a small but significant increase in FEV₁, and tryptase release, thus suggesting a KIT-dependent process and mast cells contribution to the pathobiological basis of asthma._88

Currently, further studies on imatinib in asthma are being planned in early clinical trials.

The sialic acid-binding immunoglobulin-like lectins (Siglecs), members of the immunoglobulin gene family, are currently under evaluation for future studies. They selectively regulate early neutrophil recruitment in the lung._39 Siglec-9 is expressed by human neutrophils and monocytes, as well as by a minority of natural killer cells. These proteins can interact with antibodies and glycan ligands resulting in neutrophils programmed cell death. In addition, Siglec-E antibody administration abolishes neutrophil recruitment in mouse models of neutrophil lung inflammation. As neutrophils are probably the main cause of the generation and perpetuation of inflammation in the non-Th2 endotype, targeting Siglec-9 could be useful for the treatment of severe asthma and chronic obstructive pulmonary disease (COPD)._90

**Is precision medicine already outdated?**

Severe asthma is characterized by heterogeneity and complexity and is classified according to both phenotypes and endotypes approaches. Nowadays, in contrast with the classical ‘one size fits all’ approach, precision medicine is based on specific biological profiles guided by biomarkers, which are useful for the development and selection of targeted biological therapies. As the advent of biological therapies with omalizumab, we are witnessing a growing interest in the identification of new biomarkers potentially useful for the selection and treatment guidance of patients. The choice of the right drug for the right patient is becoming increasingly important, considering the partial overlap between the populations eligible for anti-IL-5 mAbs or omalizumab, as mentioned earlier._60

Recent advances in the immunological and inflammatory asthma pathways have led to the identification of the alarmins and the key role in the pathogenesis of asthma. The airway epithelium has been shown to play a central role in the modulation of complex inflammatory processes._91,92 The cytokines produced by the epithelium can be released following the exposure to pro-inflammatory external stimuli. Among these cytokines, the triad IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) promotes immune responses and are involved in delaying the asthmatic reactions after exposure to allergens. TSLP is an epithelial-cell–derived cytokine produced after environmental and proinflammatory stimuli._93,94 The PATHWAY study further investigated the clinical and biological role of TSLP in patients with moderate-to-severe uncontrolled asthma._95 This was a randomized, placebo-controlled, dose-ranging trial for tezepelumab, a fully human first-in-class anti-TSLP mAb, where patients with various levels of blood eosinophilia were also included. The use of tezepelumab at various doses (70 mg every 4 weeks, 210 mg every 4 weeks or 280 mg every 2 weeks) showed a reduction of the exacerbation rate in the treatment groups of 61%, 71%, and 66%, respectively, as compared to the placebo group (p<0.001 for all comparisons). The same results were observed regardless blood eosinophil count, Th2 status, or FeNO levels at enrollment.

The FDA granted tezepelumab as a ‘breakthrough’ biological drug for the treatment of severe asthma, thus speeding up
its registration process. A Breakthrough Therapy definition is designed to fasten the development and regulatory review of drugs that have proven to be effective in respect of a clinically significant endpoint compared to available drugs (www.fdanews.com/articles/188355-fda-awards-astrazeneca-and-amgens-tezepelumab-breakthrough-designation).

The favorable response to this promising drug, almost completely independent of the patient phenotyping, could provocatively overcome the classic ‘tailored therapy’ or ‘precision medicine’ paradigm. However, further and much larger studies are needed to confirm these findings.

**Developments in related diseases**

In COPD, as well as in asthma, there are several inflammatory phenotypes. So far, acceptable results have only been obtained in the eosinophilic ones. In subjects with moderate-to-severe COPD and blood eosinophil counts of 300 cells/μL or greater, a major risk of exacerbations and steroids resistivity is reported.96 Two phase 3 RCTs on mepolizumab as add-on therapy in patients with eosinophilic COPD (METREX and METREO)96 showed interesting findings. Patients with a blood eosinophil count of 150 cells/μL or more at screening, or 300 cells/μL or higher during the previous 12 months were included. The results demonstrated a significant reduction (23%) of exacerbations in 25% of patients with a baseline blood eosinophil count at 300 cells/μL. The clinical efficacy was observed only in the 70% of the severe exacerbations treated with OCS.

A RCT with benralizumab, including patients with COPD and blood eosinophil higher than 300 cells/μL, is ongoing.97 A phase 3 study investigating lebrikizumab is also recruiting patients; however, given the disappointing results on severe asthma, there will probably be no favorable outcome in COPD either.81

Chronic rhinosinusitis, both CRS with nasal polyposis (CRSwNP) and without nasal polyposis (CRSsNP) is an inflammatory disease of the nose and paranasal sinuses, characterized by elevated levels of IL-5, IL-13, and eosinophils. In a randomized, double-blind, placebo-controlled study, omalizumab demonstrated positive results in patients with CRSwNP, even in non-allergic patients.98 A recent study in a real-life setting confirmed the efficacy of omalizumab in severe allergic asthma with co-existent CRSwNP.99 This is probably due to the presence of a local mucosal production of IgE. Regarding the anti-IL-5 mAbs, mepolizumab, and reslizumab, excellent results have been demonstrated especially in patients with eosinophilic nasal polyps, whereas nasal IL-5 levels did not predict a good response.40,100 Another biologic drug, benralizumab, may have the advantage of not targeting only eosinophilia but basophils, present at high levels in patients with CRSwNP.101 It will be necessary to verify through large-scale studies the real efficacy of benralizumab and its theoretical superiority over competitors.

A phase 2 study (ClinicalTrials.gov identifier: NCT01920893) demonstrated the efficacy of dupilumab in reducing nasal polyps when added to mometasone furoate nasal spray.102 Significant improvements were also observed for the SinoNasal Outcome test for sense and smell. Two RCTs are currently underway to evaluate the efficacy of this mAb in reducing the severity of nasal congestion/obstruction and endoscopic nasal polyp score (NPS) (ClinicalTrials.gov identifier: NCT02912468 and NCT02898454).

**Economic burden of asthma and biological therapies**

Asthma is a growing public health problem and the costs of management and treatment are increasing. Clinical trials have demonstrated that the control of severe asthma, which can be achieved through innovative therapies, can reduce the overall economic burden, even if the single cost of the drug increases.103 It is also shown that the cost of asthma significantly increases with the reduction of disease control. However, it is possible to obtain important savings on direct costs through the correct management of patients and the appropriate use of new therapeutic options.104

Because of the economic impact and significant increase of direct costs, the availability of new treatment options for severe asthma, such as omalizumab, bronchial thermoplasty (BT), and mepolizumab, has required great attention in the selection and management of potentially eligible patients. Moreover, in some countries, drug-economic analyses (CEAs) are necessary as a requirement to obtain the reimbursement of biological drugs, due to their high cost.105

The most considered outcomes of the published studies included exacerbations, mortality, health-related quality of life (HRQoL), use of healthcare resources, and direct costs. Most of the studies on omalizumab conclude that anti-IgE mAb achieves clinical outcomes especially when administered in patients with difficult-to-treat asthma. This drug is cost effective according to the majority of studies, especially if targeted to very severe subgroups and with price discounts.106 Direct costs could be partly offset by the reduction of the expenses incurred by the health service (e.g. hospitalizations), a reduction of indirect costs and improvement of quality of life.106

Regarding mepolizumab, there are few pharmacoeconomic data because of its recent introduction in clinical practice. An interesting CEA conducted by the ICER Group was based on a simulation model of asthma outcomes and costs in a representative population of patients eligible to mepolizumab therapy.108 The incremental cost effectiveness of mepolizumab was evaluated by gathering drug cost estimates derived from current prices and estimates of reductions in asthma exacerbations and OCS use from relevant clinical trial data. According to the authors of this analysis, based on current acquisition prices, the cost-effectiveness estimates are unfavorable, as they exceed the commonly cited thresholds.
Further doubts arise from the lack of clinical trials evaluating the long-term benefits. To obtain a value correlated to the clinical benefit, a discount of two-thirds to three-quarters from the current price list of mepolizumab would be necessary.

A recent study investigated the potential cost effectiveness of mepolizumab. A Markov model was used to determine the incremental cost per quality of life-year (QALY) obtained for mepolizumab plus standard of care (SoC) and for SoC alone. The population, including adults with severe eosinophilic asthma, was defined on a lifetime horizon. Based on the results of this study, to achieve a cost-effectiveness of about $150,000 for QALY, mepolizumab would require a discount of over 60% on the price.

So far, only one study aimed at investigating whether reslizumab can be cost effective. The authors used a Markov model to compare the cost effectiveness of add-on reslizumab with the standard of care from the US societal perspective over a 5-year time horizon. The conclusion was that the improvement in QoL and exacerbation rate with reslizumab is associated with high costs, making reslizumab unlikely to be cost-effective at the $200,000 willingness-to-pay (WTP) threshold.

Another study defined and compared the cost-effectiveness of the newest medical treatment strategies for severe refractory asthma, such as omalizumab, mepolizumab, and BT. The authors used a model including a hypothetical cohort of 10,000 patients with a 10-year horizon. In patients who are responders to biological treatment, the addition of bronchial thermoplasty was not cost-effective. Mepolizumab without BT was the most cost-effective option for biological responders. However, BT proved to be a cost-effective treatment option in the group of nonresponders to biologicals.

Conclusions

Nowadays, much more than in the past, pharmacological research has promised safe and effective therapeutic options for patients with severe, uncontrolled asthma, a very complex and heterogeneous entity. It should not be neglected that the management of severe asthma still represents a challenge, because the asthma mortality rate is still unacceptable, and because poor adherence to therapy was demonstrated not only in patients with mild symptoms, but also in those with higher levels of severity. Furthermore, acute and chronic side effects still have a major impact in those patients taking OCS treatment. Moreover, the associated costs, especially in patients that are unfit for treatment with biological drugs, are high. Some new and effective therapeutic options, such as dupilumab, will soon be available, and this will probably increase the direct costs associated with pharmacological treatment. Understanding the disease mechanisms and using predictive biomarkers will allow customization of the approach to disease management and will guide the clinician in the choice of right drug, among the increasingly numerous therapeutic options. It will reduce the number of uncontrolled patients and avoid therapeutic failures. The presence of overlapping target populations for omalizumab and anti-IL-5 requires an increasing effort in understanding the differences among the underlying pathways of these molecules. It is increasingly clear that omalizumab remains the gold standard for refractory allergic asthma, especially for the ‘early onset’ phenotype, while anti-IL-5 mAbs are indicated in eosinophilic asthma with comorbidities such as nasal polyposis. Among the latter, benralizumab seems to have a small advantage linked to its peculiar mechanism of action, to its rapid onset of effect, and to the greater steroid-sparing effect, as discussed earlier. Beyond indirect evaluations, comparative head-to-head studies will be essential to allow a correct treatment choice and to avoid empirical or marketing-oriented selection strategies. However, non-Th2 endotype asthma remains a major challenge, as research has not provided so far so many treatment options. In the future, the phenotype will obtain the focus it deserves.

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REVIEW – Treatments for severe asthma


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