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RESEARCH ARTICLE

Pharmacologic Treatment of Type 2-High Severe Asthma

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ABSTRACT

Asthma is a common and heterogeneous disease whose treatment has considerably changed over the last decades. While inhaled therapies based on inhaled corticosteroids and long acting β2 agonists are effective in controlling asthma in the majority of patients, about 5% of asthmatics poorly respond to inhaled steroids or inhaled steroids/long acting β2 agonists combinations. These patients are affected by "severe asthma", which is associated with need of oral corticosteroids, progression of the disease, increased use of healthcare services, deterioration of quality of life, and a significant economic burden on society. Asthma is no longer considered a single disease, but a respiratory syndrome with complex biological network of distinct and interrelating inflammatory and remodeling pathways (endotypes) that are associated with different clinical manifestations (phenotypes) both in the lungs (asthma) and other organs (e.g. nose and skin). Severe asthma endotypes may be broadly regarded as Type 2-high and Type 2-low, a model that has become central to asthma management with the development of novel treatments for the Type 2-high endotypes. The hallmark feature of Type 2-high asthma is eosinophilic inflammation, often associated with increased serum IgE, increased exhaled nitric oxide (FeNO) and blood eosinophilia. The discovery of the main key drivers of Type 2-high inflammation (IgE, cytokines such as interleukin IL-5, -4 and -13) enabled the development of new biological agents directed towards specific molecular targets. These advances have shifted the existing paradigm "one drug fits all" to "patient-tailored" novel therapies. The monoclonal antibodies direct to IgE (omalizumab), IL-5 and IL-5 receptor (mepolizumab, benralizumab, reslizumab), and to the α chain of the IL-4 and IL-13 combined receptor (dupilumab), and more recently, to the thymic stromal lymphopoietin (tezepelumab) have been shown in both clinical trials and real-life studies to control symptoms, reduce asthma exacerbations and improve lung function in severe asthmatics not controlled by full inhalation therapies. More recently, the Single Inhaler Triple Therapy (SITT) containing inhaled steroids, long acting β2 agonists and muscarinic antagonists has been developed, slightly improving the effectiveness/safety of the inhalation therapy. This report aims to review available therapeutic opportunities for patients with severe asthma focusing on patients with Type 2-high severe asthma and how to position these new therapeutic alternatives in clinical practice.

Keywords: Biologics, monoclonal antibodies, lung function, exacerbations, airways inflammation.

Introduction

Asthma is a heterogeneous disease characterized by variable symptoms of breathlessness, cough, chest tightness, and wheeze.[1] Asthma represents an important global health problem and involves all age groups; it affects about 300 million people globally, with figures constantly on the rise. Since asthma is primarily an inflammatory disorder of the airways, inhaled corticosteroids (ICS) alone or in combination with inhaled bronchodilator long acting β2 agonists (LABA) are the cornerstone of asthma management. While inhaled therapies are effective in providing good control of asthma in the majority of cases, up to 5% of asthmatic adults have difficult to treat asthma or severe asthma with an increased risk of developing fixed airflow limitation, exacerbations, oral corticosteroids use (OCS), hospitalization and in exceptional cases even death.[2] Severe asthma should be distinguished from difficult-to-treat asthma.[3] Indeed, in difficult-to-treat asthma poor control is often due to treatable traits such as scarce adherence to inhaled glucocorticoids, incorrect inhaler technique, and coexisting comorbidities or inadequate behaviours (i.e. smoking or diet).[4] Severe asthma is instead defined severe when control remains poor despite measures that adequately address these factors.[5] In particular, severe asthma is defined as "asthma that requires treatment with high dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy".[6] Severe asthma imposes an unacceptable burden on patients' quality of life, healthcare systems, and society through loss of productivity that has implications for the economy and quality-adjusted life years.[1] For these patients there is a need for innovative therapies and the recent advances in the identification of at least two distinct molecular pathways of airway inflammation, named Type 2-high and Type 2-low, enabled the development of new biological agents directed towards specific molecular targets. While in the last two decades biological therapies targeting Type 2-high inflammation have been successfully developed, little progresses have been done in Type 2-low asthma. Our review will examine the available pharmacological opportunities for patients with Type 2-high severe asthma, starting from the inflammatory mechanisms underlying its pathogenesis up to the latest drugs with desirable efficacy also in patients with Type 2-low asthma, such as tezepelumab and single inhaler triple therapy.

Inflammatory endotypes

The clinical heterogeneity of asthma is due to distinct complex molecular mechanisms, identified as endotypes. More than 20 years ago, Wenzel et al.[7] suggested two different pathologic endotypes underlying the severe asthma phenotype, based on the presence of airways eosinophils. Following this concept, severe asthma endotypes are classified as Type 2-high (eosinophilic) and Type 2-low (non-eosinophilic).[8] These different types of inflammation result from different immune response driven by CD4+ T cells, Th1 and Th2. Th1 cells stimulate phagocytic activity, while Th2 cells focus on eosinophilic activity and IgE production.[9]

Type 2-high and Type 2-low inflammatory responses are both triggered by an epithelial barrier defect resulting in a weakening of defences against environmental stimuli such as viruses, bacteria, smoking and allergens. This causes an altered epithelial signalling with the production of key cytokines such as thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25) and interleukin -33 (IL-33), termed "alarmins". The production of alarmins, due to allergens exposure, drives the maturation of CD4+ T-cells to induce a Th2 adaptive immune response. Th2 cells, as well as the innate lymphoid cells 2 (ILC-2) activated by the upstream mediators, produce a variety type of cytokines such as IL-4, IL-5, IL-13, responsible of the Type 2-high inflammation.[10,11] However, alarmins like TSLP are also involved in the pathogenesis of Type 2-low inflammation (via IL-17) through the differentiation of Th17 cells, the activation of mast cells, basophils, natural killer T cells, innate lymphoid cells, neutrophils as shown in figure 1 .[5,12–14]

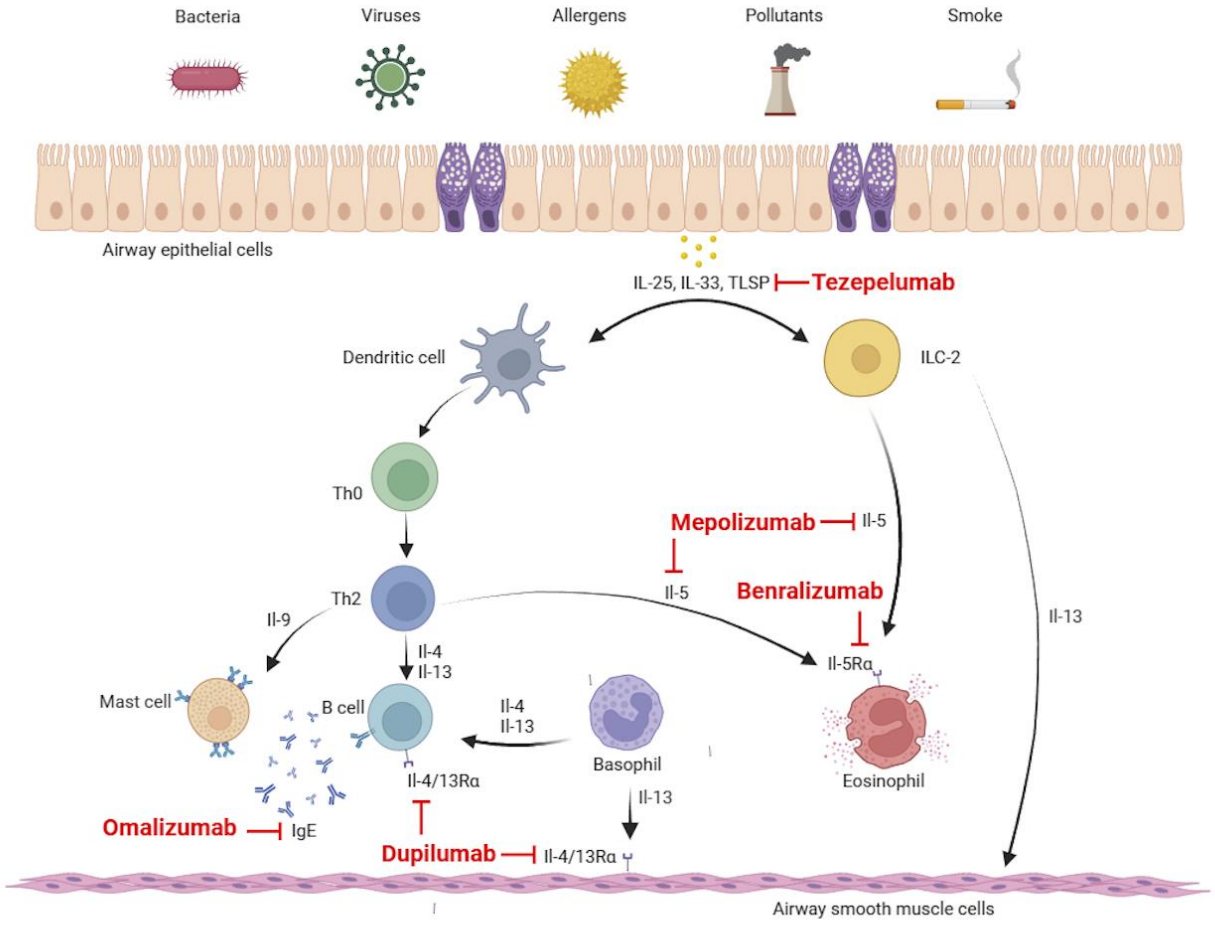

Figure 1. Immunopathogenesis of severe Type-2 high asthma and molecular targets of add-on biologic treatments. Th0 (T-helper 0 cells), Th2 (T-helper 2 cells), ILC-2 (Innate lymphoid cells 2), B-cell (B lymphocytes). This original figure was created by the authors using BioRender.com

Type 2-high inflammation underlies the most important asthma hallmarks, such as mucus hypersecretion, bronchial remodeling, subepithelial fibrosis and airway hyperresponsiveness. This can be explained by the activation of mast cells, basophils and eosinophils as effector cells releasing pro-inflammatory mediators like histamine, leukotrienes and prostaglandin D2, as well as the production of the cytokines themselves. Moreover, Type 2-high inflammation mediates the B-cell switching in production of IgE.[11,15]Among Type 2-high cytokines, IL-5 is responsible for the growth, differentiation, recruitment and activation of eosinophils while IL-13 for smooth muscle cells proliferation and contractility. Interleukin-4 together with IL-13 play a key role in bronchial remodeling, B cell class switching for IgE production, differentiation of naïve CD4+ T cells into the Type 2-high phenotype and in the production of FeNO in airway epithelial cells by upregulating inducible nitric oxide synthase (iNOSs).[16–18] Additionally, IL-13 is responsible for the chronic mucus hypersecretion through an epigenetic mechanism causing the transition of the airway epithelial cells into mucus secreting phenotype.[19] This mechanism is important to understand since the persistent mucus plug is correlated with a higher likelihood of exacerbation rate and increase of mucus plug is negatively correlate with lung function and positively correlate with global measures of air trapping.[20]

Biomarkers

One of the cornerstones of research on inflammatory mechanisms is the identification of biomarkers that can best identify the different asthma endotypes in clinical practice.

Type 2-high inflammatory biomarkers include sputum and blood eosinophils, FeNO and total IgE serum level.[1] While GINA 2023 suggests blood eosinophil count ≥150 cells/μL, FeNO ≥ 20 ppb and sputum eosinophils ≥ 2% as cutoff predicting Type 2-high inflammation, data in literature are still controversial. Popovic et al.[21] indeed found a sputum eosinophil cut off > 3% as a biomarker to distinguish eosinophilic versus neutrophilic (or Type 2-low) asthma, while Woo et al.[22] validated blood eosinophil count ≥300 cells/μL and FeNO ≥ 25 ppb as candidate biomarkers for patients with Type 2-high asthma who may require biologics. Indeed, to date the blood eosinophils cut off ≥300 cells/μL is used to prescribe anti eosinophils biologics (mepolizumab and benralizumab), and clinical trials and real-life studies showed that patients with eosinophil count above this value are the best responders to anti-eosinophils biologics.[23,24]

Nowadays, total serum IgE is approved as biomarker for determining eligibility in severe allergic asthma patients for anti-IgE biologic therapy, however its role as biomarker of Type 2-high inflammation is still debated. Indeed, patients with Type 2-high severe asthma may have both high IgE serum level and high blood eosinophil count, making it difficult to understand the real driver of inflammation in view to prescribe the more appropriate biologic (e.g. anti-IL-5/IL-5Rα or anti IgE or anti IL-4/13 Rα). Moreover, Ricciardolo et al.[25], exploring the role of IgE level among Type 2-high and Type 2-low phenotypes, showed high IgE levels even in patients with Type 2-low asthma, suggesting that high total serum IgE confer different clinical profile in both phenotypes. Thus, total serum IgE level is not useful to predict Type 2-high asthma, but for clustering asthma towards forms with overlapping pathogenetic mechanisms. Finally, Denton et al.[26], analyzing 1175 Type 2-high severe asthmatic patients with pre-specified thresholds (total serum IgE >75 kU/L, blood eosinophil count >300 cells/μL and FeNO>25 ppb), found consistent overlap in biomarkers suggesting that, currently, a single biomarker is not able to discriminate different inflammatory pathways to reach a personalized treatment.

Unfortunately, very much less is known about pathogenesis of Type 2-low asthma. This endotype encompasses both neutrophilic asthma mediated by IFN and/or IL-17 immune response with sputum neutrophilia (> 40-60%,) and a pauci-granulocytic non inflammatory disease with normal sputum levels of both eosinophils and neutrophils, but no biomarker has yet been identified.[8,27,28]

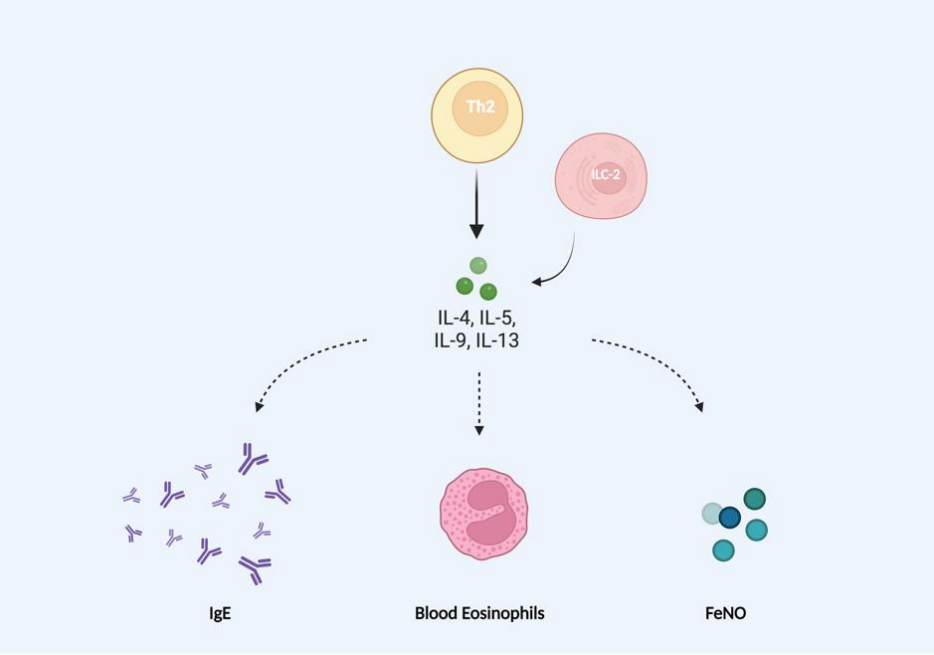

Figure 2. Type-2 high biomarkers. Blood eosinophils and FeNO are two criteria to define Type-2 phenotype, while IgE is a biomarker used for the eligibility to anti-IgE. FeNO (fractioned exhaled nitric oxide), Th2 (T helper 2 cells), ILC-2 (Innate lymphoid cells 2). This original figure was created by the authors using BioRender.com

Pharmacological management of severe asthma

A significant number of asthmatic patients, after assessment of good adherence to inhaled glucocorticoids, correct inhaler technique and controlled coexisting comorbidities and behaviors, remain uncontrolled despite medium or high-dose ICS/LABA. The addition of a long-acting muscarinic antagonist (LAMA), before escalating to biologic agents or oral corticosteroids, has been recommended by GINA report since 2015.[29] Evidences in literature have shown that ICS/LABA/LAMA single-inhaler triple therapy (SITT) is a safe and effective therapeutic alternative in these patients, and the dose of ICS may differ on the basis of endotype (e.g. eosinophilic vs non–eosinophilic) and clinical phenotype (e.g. presence of airflow limitation and /or exacerbations history).[30] Indeed, even though it has not yet been proven if specific phenotype could benefit more from triple-inhaler therapy, SITT might be taken into consideration for patients with low Type 2 markers and uncontrolled asthma despite medium-dose ICS/LABA as an alternative to high-dose ICS/LABA as well as for patients with uncontrolled asthma despite high-dose ICS/LABA and persistent airflow limitation, before escalating to OCS or biologic treatment. [31]

Single inhaler triple therapy

Long-acting muscarinic antagonists act by blocking muscarinic acetylcholine receptors (mAchR) on the airway smooth muscle cells, epithelial cells, and submucosal glands. Acetylcholine (Ach) is a neurotransmitter synthesized both by parasympathetic nerve fibres and airway epithelial cells. Five muscarinic receptors have been identified, although only M1, M2, M3 receptors are involved in airway diseases. Binding to M1 and M3 receptors, Ach causes bronchoconstriction, mucus secretion, airway inflammation and remodelling. M2 receptors, instead, are expressed mainly on presynaptic parasympathetic neurons and act as auto-receptors limiting the release of Ach and its effect downstream.[32] The effects of LAMA on airflow obstruction are synergic with those of ICS/LABA[33], increasing bronchodilation. Moreover, the mechanism of action of LAMA is independent by Type-2 high or Type-2 low inflammation.[34]

Among LAMA, tiotropium (TIO) was the first approved as add-on treatment to ICS/LABA.[29]. In severe asthmatic patients with fixed airflow obstruction (post-bronchodilator $FEV_1 \leq 80$ % predicted value and $FEV1/FVC \leq 70$ %) and at least one severe exacerbation in the previous year, add-on tiotropium significantly improved lung function (measured as peak FEV_1 and pre-dose FEV_1) and increased the time to the first severe exacerbation[35,36]. Subsequently, different clinical trials investigated the role of SITT in asthma, focusing on the benefits on lung function, exacerbations, and quality of life. We reviewed five phase III RCTs: TRIMARAN combined with TRIGGER [37], IRIDIUM[38], ARGON[39], and CAPTAIN[40]. TRIMARAN and TRIGGER were the first studies investigating the efficacy and safety of single-inhaler beclomethasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium (GLY) in patients with uncontrolled asthma and history of frequent exacerbations. In TRIMARAN patients were randomly assigned to receive medium-dose BDP/FF/ GLY or the same medium-dose BDP/FF. In TRIGGER patients were randomly assigned (2:2:1) to receive high-dose BDP/FF/GLY or the same high-dose BDP/FF, or open-label BDP/FF plus tiotropium. Compared with the respective BDP/FF groups, patients under SITT had an increase in pre-dose FEV_1 of 57 mL in TRIMARAN and of 73 mL in TRIGGER, with a reduction in the rate of moderate and severe exacerbations of 15% in TRIMARAN and 12% in TRIGGER. No significant differences were found between the open and closed treatment combinations in TRIGGER.

IRIDIUM compared the efficacy of once-daily SITT with medium- or high-dose mometasone furoate (MF), indacaterol acetate (IND), and glycopyrronium bromide (GLY) with two different ICS/LABA combinations, respectively once-daily MF/GLY (on medium- or high-dose) and high-dose twice daily fluticasone propionate/salmeterol (FP/SLM). At 26 weeks, a greater increase in though FEV_1 (primary outcome) was reported with both medium- and high-dose MF/IND/GLY in comparison with ICS/LABA groups. Furthermore, despite an overall non-significant reduction of exacerbation rate of MF/IND/GLY vs MF/IND, treatment with high-dose MF/IND/GLY was correlated to reductions of 36% in moderate or severe exacerbations and 42% in severe exacerbations compared to high-dose FP/SLM.

Afterwards, ARGON compared once-daily SITT with medium- or high-dose MF/IND/GLY with high-dose FP/SLM plus TIO. The primary outcome was to evaluate the non-inferiority of the closed triple combination in terms of Asthma Quality of Life Questionnaire (AQLQ). At 24 weeks, the primary outcome was met for either MF/IND/GLY medium- or high-dose to high-dose FP/SLM + TIO. Moreover, high-dose MF/IND/GLY significantly improved trough FEV1 by 96 mL and significantly reduced the risk of moderate exacerbations (rate ratio 0.57)

versus high-dose FP/SLM + TIO.

In CAPTAIN, once-daily SITT with fluticasone furoate (F)/umeclidinium (UMEC)/vilanterol (VI) significantly improved lung function (primary outcome) and symptoms, but did not reduce the rate of moderate/severe exacerbations versus F/VI group, even though it should be noticed that a history of exacerbations in the previous year was not an inclusion criterion in the study. However, it was also noticed that higher doses of ICS were related to fewer exacerbations and higher FEV_1 in patients with biomarkers of Type-2 inflammation (high blood eosinophil or FeNO). These data have been analysed in a network meta-analysis by Rogliani et al.,[30] in which SITT with high-dose ICS confirmed to be more effective in reducing moderate/severe exacerbations and improving lung function as compared both to SITT with medium dose-ICS and medium/high-dose ICS/LABA therapy. Another recent systematic review and meta-analysis by Kim et al.[41] analysed the role of ICS/LABA/LAMA vs ICS/LABA showing that SITT was associated with a reduction in number of exacerbations and an improvement in asthma control, without significant differences on quality of life and mortality.

Among the greatest expected advantages of SITT there are the improved treatment compliance and adherence when compared with open-triple therapy, through a reduction in dosing and handling errors.[42] On the other hand, it could be argued that a triple fixed combination limits flexibility in the dose adjustments of the single components and it's still debated if SITT is always indicated in patients before escalating to biologics.[31] Indeed, it's not yet clear which phenotypes may best benefit from triple inhaler therapy, in particular SITT. Likely, the best responders could be patients with persistent airflow limitation, as suggested from a post-hoc analysis of the TRIMARAN and TRIGGER trials.[43]

Biologics

Patients with severe uncontrolled asthma despite optimized inhaled therapy require a clinical and biological characterization to identify underlying endotype in order to find the best tailored treatment with available biologics.[1,44] The five approved monoclonal antibodies effective in Type 2-high severe asthma are omalizumab targeting IgE, mepolizumab, benralizumab and dupilumab targeting respectively IL-5, IL-5 Rα and, IL-4/IL-13 Rα and tezepelumab targeting thymic stromal lymphopoietin.[5]

OMALIZUMAB

Omalizumab was the first biologic agent approved for use in moderate-to-severe asthma in 2003 by the Food and Drug Administration (FDA) and gained marketing authorisation in Europe in 2005. Omalizumab is a recombinant humanised monoclonal antibody (IgG1) anti-IgE that binds circulating IgE, preventing its interaction to the receptors of mast cells and basophils, and blocking the release of histamine and other inflammatory mediators.[5,45]

Over nearly 20 years, several studies have assessed the efficacy of omalizumab in patients with severe allergic asthma. The first two randomized clinical trials (RCTs) conducted by Solèr et al.[46] and Busse et al.[47] showed that patients with severe allergic asthma on omalizumab had fewer asthma exacerbations, and a greater likelihood of ICS dose reduction or discontinuation than the placebo group. The INNOVATE [48] was the third, multicentre randomized, placebo-controlled, double-blind trial assessing the efficacy of omalizumab in patients with uncontrolled asthma, despite GINA step 4 therapy. In the study were enrolled 419 subjects with a proven allergy to at least one perennial allergen, an impaired lung function (predicted Forced Expiratory Volume in the first second, FEV_1 of 40–80%), and a recent history of severe exacerbations despite high doses of ICS/LABA and other control agents. Over 28 weeks the clinically significant asthma exacerbation rate (primary outcome) resulted 26% lower in the active treatment arm compared with the placebo group. Moreover, omalizumab improved asthma-related quality of life, morning peak expiratory flow and asthma symptom control. In the EXALT study[49], omalizumab significantly reduced OCS intake in patients receiving maintenance prednisone at baseline, compared to placebo. Finally, EXTRA[50] and EXCELS[51] are two relevant post-marketing studies investigating the role of biomarkers in predicting the response to omalizumab, and the safety with respect to cardiovascular or cerebrovascular diseases. The EXTRA showed that high levels of FeNO, blood eosinophil count (BEC), and serum periostin at baseline are associated to a reduction of asthma exacerbations. In the EXCELS study the slightly increase of serious cardiovascular and cerebrovascular effects reported in treated group was not definitely related to the treatment. Finally, most of the real-life studies, such as the EXPERIENCE[52], RELIEF[53] and STELLAIR[54] endorsed the results of previous RCTs. Both the EXPERIENCE in 2013 and the RELIEF in 2022 confirmed the effectiveness and safety of omalizumab in reducing exacerbations, symptoms, healthcare utilization, rescue medication use, and OCS use. The STELLAIR study, a retrospective real-life study investigating the importance of pre-treatment blood eosinophil count as a predictive factor for response to

omalizumab, showed that a large proportion of patients with severe allergic asthma have a blood eosinophil count ⩾300 cells/μL however, omalizumab effectiveness was similar in "high" and "low" eosinophil subgroups. These findings confirm those already published by the EXTRA[50] and INNOVATE[48] studies that showed similar exacerbation rates during omalizumab treatment in low and high eosinophil subgroups.

To date omalizumab represents an add-on maintenance treatment of adults and children 6 years of age or older with moderate to severe persistent asthma who have high serum IgE levels (30–1300 IU/mL in the United States, of 30–1500 IU/mL in Europe), a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS/LABA. Other than in allergic asthma, omalizumab now is also indicated in chronic rhinosinusitis with nasal polyposis (CRSwNP), when uncontrolled with inhaled corticosteroids[55] and in chronic spontaneous urticaria.[56]

ANTI INTERLEUKIN-5 MONOCLONAL ANTIBODIES

Since interleukin-5 is the main cytokine involved in the Type 2-high inflammation, monoclonal antibodies targeting this interleukin and its receptor, mepolizumab and benralizumab respectively, have a key role in the treatment of eosinophilic severe asthma.

MEPOLIZUMAB

Mepolizumab was approved in 2015 by the FDA as an add-on treatment for uncontrolled severe eosinophilic asthma. Later, it has also been approved for eosinophilic granulomatosis with polyangioitis (EGPA), hyper eosinophilic syndrome (HES) and chronic rhinosinusitis with nasal polyps.

Mepolizumab is a humanized IgG1/κ monoclonal antibody which selectively binds circulating IL-5 and inhibits IL-5 signalling, thereby reducing the production and survival of eosinophils.[57,58]

In 2007 Page et al.[59] conducted the first study on the efficacy of intravenous infusion of mepolizumab in 362 asthmatic patients with persistent symptoms despite high steroids inhaled therapy. Even though mepolizumab significantly reduced blood and sputum eosinophilia, no benefits were found on clinical outcomes such as lung function, symptoms, use of rescue medication and quality of life and even on exacerbations (secondary outcomes). However, the 50% reduction in exacerbations in the mepolizumab group compared with placebo group lead to the hypothesis that airway eosinophilia is more associated to exacerbations rate than to other clinical outcomes like lung function and /or symptoms.[7,60]. Indeed, when Haldar et al. and Nair et al.[61,62], in their successive studies, enrolled patients with severe eosinophilic asthma (high blood and sputum eosinophil count) and history of frequent exacerbations despite high doses of ICS/LABA and/or OCS, were able to show a significant reduction of severe exacerbations, of OCS use and some improvements in symptoms scores and lung function confirming the strong link between eosinophilia and asthma exacerbations.

Mepolizumab efficacy and safety were successively confirmed by several RCTs. DREAM[23] was the first RTC enrolling 616 severe asthmatic patients selected on the evidence of eosinophilic inflammation through increased sputum and/or blood eosinophil count, increased FeNO, worsening of asthma control after reduction of ICS and/or OCS and, more importantly, with a history of frequent severe exacerbations (≥ 2) requiring OCS in the previous year. The study showed the efficacy of mepolizumab in reducing asthma exacerbations, highlighting once again how baseline peripheral blood eosinophil count and exacerbation frequency were the most important predictive factors of response to mepolizumab. The shorter MENSA study[63], enrolling 576 patients with severe eosinophilic asthma and frequent exacerbations, confirmed the data reported by DREAM on the reduction of exacerbations. Moreover, an improvement in FEV_1, quality of life and symptoms control was also shown. Focusing on OCS sparing, the SIRIUS study[64] conducted in asthmatic eosinophilic patients on systemic systemic steroids therapy, showed a 50% reduction from baseline in glucocorticoid daily dose in mepolizumab group compared with placebo group. Additionally, patients on mepolizumab experienced a reduction in number of exacerbations despite a reduced OCS dose. The efficacy of mepolizumab over time was confirmed by subsequent open-label extension studies COSMOS, COSMEX and COLUMBA, enrolling patients from previous phase III clinical trials. COSMOS[65], a 52-week open label extension study enrolled 651 patients (91% from MENSA and 93% from SIRIUS), showed persistent effects of mepolizumab in lowering exacerbation rate and OCS sparing in the patients already treated. Patients on placebo in MENSA and SIRIUS initiating mepolizumab showed improvements in all outcomes like those in active treatment in the 2 previous studies. Interestingly, in COSMEX[66], a 172 weeks extension study enrolling patients from COSMOS, about 45% patients definitely stopped OCS treatment. Finally, the COLUMBA[67] study, enrolling patients from DREAM, showed the long term

efficacy of mepolizumab in reducing exacerbations in a population followed for at least 3.5 years.

Interestingly, studies in real life confirm results of clinical trials. While the REALITY A[68] proved that mepolizumab is able to reduce the dose, or even suspend, the maintenance OCS (mOCS) in corticosteroid-dependent patients with a significative reduction in exacerbation rate, the REDES study[69] confirmed the reduction of exacerbation rate (by 77.5%), the improvement in FEV_1 (about 0.21 L) and in asthma symptoms control (Asthma Control Test ACT +6.7 points) and the OCS discontinuation at 12 months of treatment.

Few data regarding the effect of mepolizumab on airway remodeling are available. After the study by Haldar et al.[61] showing a reduction of airway-wall thickness measured by computer tomography (CT) after 12 months of treatment with mepolizumab, in MESILICO[70], preliminary data on bronchial biopsies performed before and after 12 months of treatment showed that 1 year treatment with mepolizumab is enough to reduce the membrane thickness, airway smooth muscle area, epithelial damage, and tissue eosinophil number suggesting a role of mepolizumab in reducing airways remodeling.

About the opportunity of biologic withdrawal is an emerging issue, but nowadays there are more evidence against suspending versus continuing therapy, as shown in the COMET study. [71]

BENRALIZUMAB

Benralizumab was approved in 2017 by the FDA as an add-on treatment for uncontrolled severe eosinophilic asthma. Benralizumab is a humanized IgG1/κ monoclonal antibody that binds the fraction α of IL-5 receptor with his Fab fragments, whereas the constant fragment (Fc) interacts with FcγRIIIa receptors on the membrane of natural killer (NK) cells.[72] After this interaction, NK cells release proapoptotic proteins (perforin and granzyme B) which activate antibody-dependent cell-mediated cytotoxicity, leading to a final effect of eosinophils apoptosis.[73]

SIROCCO[74] was the first RCT conducted on 1205 severe asthmatic patients with at least two exacerbations in the previous year despite high ICS/LABA treatment. Patients were stratified by blood eosinophil count > or < 300 cells/μL, and randomly assigned to benralizumab 30 mg every 4 weeks (Q4W), every 8 weeks (Q8W) or placebo every 4 weeks, for a total duration of 48 weeks. In patients with BEC > 300, the annual exacerbation rate (AER) reduction was successfully achieved in both treatment groups versus placebo (-45% and -55%, respectively). Secondary outcomes like improving pre-bronchodilator FEV_1 and asthma symptoms control were also achieved, even if asthma symptoms reduction was significant only in the Q8W regimen. In patients with BEC < 300 cells/μL the primary outcome was achieved only in the Q4W regimen, while no response has been shown on secondary outcomes, confirming the role on benralizumab in the eosinophilic inflammation. The same results were observed in the CALIMA study[75], enrolling 2505 patients stratified on blood eosinophil count with 300 cell/μL as cut-off. ZONDA trial[76] highlighted the OCS sparing effect of benralizumab in 220 severe asthmatic patients with BEC >150 cells/μL and on OCS for at least 6 months before enrollment despite the regular treatment with ICS/LABA. The study demonstrated a reduction of median final oral glucocorticoid dose from baseline by 75%, compared with a reduction of 25% in the placebo group at 28 weeks.

The safety and long-term efficacy of benralizumab were confirmed by subsequent open-label extension studies, BORA and MELTEMI.[77,78] BORA enrolled 1926 patients who had completed the SIROCCO, CALIMA and ZONDA trials for a total duration of 56 weeks for adult patients. However, patients from the ZONDA study were excluded in final analysis because the trail was shorter and smaller than SCIROCCO and CALIMA. MELTEMI enrolled patients who at least completed 16-40 weeks of active treatment in BORA. In 384 patients who completed the study, no serious adverse events were reported in the 4 up to 5 years duration of the study. Patients on treatment in previous trails maintained the reduction of blood eosinophils and the reduction of asthma exacerbations, while among patients in placebo after initiating benralizumab in BORA, median BEC reached 0 cells/μL and AAER were similar across treatment groups.

PONENTE[79] was the first study aimed to investigate the OCS tapering in patients with steroid dependent severe asthma monitoring adrenal function. The study enrolled 598 asthmatic patients with BEC> 150 cells/μL at enrolment or > 300 cells/μL in the previous year, treated with maintenance OCS for at least 3 months before the study. Results showed that about 60% of patients had a complete or partial adrenal insufficiency. Using a personalized OCS dosage-reduction algorithm, while initiating benralizumab, the study proved that 82% of patients reduced OCS intake to 5 mg or less, and 62.8% of these completely

discontinued OCS. Moreover, about 30% of patients with adrenal insufficiency restored gland function.

The post hoc analysis of CALIMA and SCIROCCO[24], analyzing baseline clinical factors related to benralizumab efficacy, showed that the greater responders to benralizumab in term of improvement of AER, lung function and symptoms control are patients with BEC > 300 cells/μL, OCS use, FVC<65% of predicted and nasal polyposis as comorbidity.

Real life studies confirm results of clinical trials. ANANKE[80], an Italian multi-center retrospective cohort, enrolled patients with SEA Severe Eosinophilic Asthma on benralizumab for at least three months. Median treatment duration was 9.8 months. As primary endpoint the study described patient's characteristics such as comorbidities, total IgE and BEC, lung function, symptoms control, number, and severity of exacerbations in the 12 months before treatment, healthcare resource utilization, maintenance treatments and biologics during the previous year. The characteristics of the population reflect the phenotype already described as better responder to benralizumab by the post-hoc analyses of SCIROCCO and CALIMA. Indeed, analyzing the cohort receiving benralizumab in this real-world setting, among 205 severe eosinophilic asthmatic patients, 53.7% had nasal polyposis, 25.9% were OCS users, 15.3% presented ≥ 3 exacerbations/ year and median BEC and FEV_1 were respectively of 589 cells/μL and 70.6% +- 21.6% predicted. The description of the outcomes concerning the period of treatment was the secondary endpoint of the study. In particular, analysis performed on 205 enrolled patients showed a BEC fall to 0 at week 16 of treatment, zero exacerbations in the 81% of patients, a 50% reduction and 43.2% interruption of OCS intake in OCS-dependent at baseline, a reduction of health care resource utilization and an improvement in lung function and in asthma control during the observation period. Subsequently, data on 162 severe eosinophilic asthma (SEA) patients were collected over a period of at least 96 weeks with a median exposure to treatment of 98.4 weeks, showing how benralizumab was able to maintain an important reduction of AER over time (94.9%), to eliminate OCS use (60% of patients), while improving lung function (median increase in pre-BD FEV_1: +400 ml) and ACT score (median score: 23), with a nearly complete depletion of BEC.[81]

Lastly, the post hoc analysis of ANANKE[82–84] focused on the best responding asthmatic phenotype to benralizumab, highlighting how a BEC in a range of 300-450 cells/μL and nasal polyposis as comorbidity could be valid indicators of response to treatment, regardless a history of previous biologic therapy. In particular, the efficacy of benralizumab in patients with SEA and nasal polyps confirmed previous data from the ANDHI trial.[85] Interestingly, an improvement of work productivity and activity during treatment with benralizumab has been shown in 137 asthmatic patients from the Dutch Register of Adult Patients with Severe Asthma for Optimal Disease management (RAPSODI)[86], confirming the effectiveness on the quality of life.

Nowadays, biologics are prescribed as add on high inhaled therapy, even though many efforts are focusing on the reduction in maintenance ICS/LABA therapy for patients treated with monoclonal antibodies.[87] Jackson D.J et al. in SHAMAL study[88] find that 92% of patients well-controlled on benralizumab were able to reduce their ICS/formoterol dose by week 32, and most of them (92%) were exacerbation free during the reduction period. The authors conclude that severe asthmatic patients, achieving clinical stability with inhaler and biological treatments, may be able to step down ICS/LABA.

DUPILUMAB

Dupilumab was approved in 2017 by the FDA, initially for severe atopic dermatitis[89], from 2018 as add-on maintenance treatment for adult and pediatric patients aged 6 years and older with moderate-to-severe Type 2-high asthma with high blood eosinophil count (>150 cells/μL) and FeNO (>25 ppb). Later it was also approved in adults with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)[90], that often occurs as asthma comorbidity, sharing the similar inflammatory pathway.[91]

Dupilumab is a recombinant human IgG4 monoclonal antibody that binding the alpha subunit of the interleukin-4 receptor (interleukin-4Rα) prevents the dual signaling of interleukin-4 (IL-4) and interleukin-13 (IL-13).[92] Interleukin-4 and IL-13 bind to different but shared receptors. Specifically, the type I receptor (IL-4Rα/γc), exclusively responsive to IL-4 stimulation, is primarily localized on lymphocytes and regulates the differentiation of Th2 cells. Conversely, the type II receptor (IL-4Rα/IL-13Rα), responsive to both IL-4 and IL-13, demonstrates widespread expression on airway structural cells such as goblet cells, fibroblasts and smooth muscle cells, leading to a reduction of mucus

plug, proliferation and contractility of bronchial smooth muscle and bronchial remodeling, thus to an improvement of asthma control.[93]

Different clinical trials support the use of dupilumab for severe Type 2-high asthma. The first pivotal study investigating the efficacy of dupilumab was conducted in 52 adults with uncontrolled persistent asthma and elevated BEC (≥300 cells/μL) or an elevated sputum eosinophils level (≥3%) showed a significant reduction in the exacerbation rate and an improvement in lung function and asthma control, compared to placebo.[94] In the phase 2b dose-ranging trial, designed to investigate the effect of dupilumab on lung function, the results showed an increasing of FEV_1 from baseline at week 12 in patient with baseline BEC of at least 300 cells/μL, however similar effects were observed for the overall population irrespectively of baseline eosinophil count. Moreover, in this population dupilumab reduced severe exacerbation rate.[95]

Dupilumab received the approval after the 2 phase 3 randomized double-blind clinical trial. The LIBERTY ASTHMA QUEST study[96] showed a 47,7% lower rate of severe asthma exacerbations among patients assigned to 200 mg of dupilumab every 2 weeks vs placebo, as well as better lung function, asthma control and a reduction in Type-2 biomarkers. In the LIBERTY ASTHMA VENTURE designed to evaluate the OCS sparing[97], dupilumab significantly reduced OCS dose (mean 70%, vs placebo) at week 20 to 24 in OCS-dependent patients, maintaining asthma control, improving lung function and reducing the risk of severe exacerbation rate, irrespectively of baseline eosinophil level or other biomarkers of Type 2-high inflammation. This study provided also long-term safety profile in which the most common adverse event was the blood hyper-eosinophilia (up to ≥5000 cells/μL) which occurred at a higher frequency in the dupilumab groups compared to placebo. Blood eosinophil count increased transiently following dupilumab treatment and returned to baseline levels at week 24 without leading to additional adverse events. Nevertheless, a minority of patients with pre-existing systemic eosinophilic conditions, manifested clinical symptoms and eosinophilic pneumonia.[98]

The long-term safety and efficacy of dupilumab have been confirmed in the TRAVERSE open label extension study, on 2282 patients from previous QUEST and VENTURE studies followed for 148 weeks. The most frequently reported adverse events were nasopharyngitis (17.5–25.9%), injection site erythema (2.2–23.4%), and bronchitis (9.3–19.0%). Serious asthma exacerbations (0.5–3.6%) and pneumonia (0.7–2.7%) were the most frequently reported serious adverse events.[99]

Finally, real-life studies confirmed the effectiveness and safety of dupilumab showed in the RCTs. The significant improvement in symptoms, lung function and reduction of OCS intake and exacerbation rate after only 3 months of treatment with dupilumab reported in an early and small study of 38 patients [100], were confirmed by a larger real-life cohort study conducted on 64 severe asthmatic patients followed for 12 months.[101] In both studies a transient increase in the eosinophil count was observed in few patients (≥1000 cells/μL in 2 cases in the first study and ≥1500/in 16 patients in the latter), however no clinical consequences were reported. A larger recent retrospective multicenter observational study on 127 severe asthmatic patients of which the 61% presented with CRSwNP, reported no exacerbations with an improvement of both ACT and Sino-nasal Outcome Test 22 (SNOT-22) with reduction of daily steroids intake.[102]

TEZEPELUMAB

Tezepelumab is the last monoclonal antibody approved by the FDA in 2021 for the treatment of patients with uncontrolled severe asthma. It is a human monoclonal IgG2 antibody that specifically binds to the alarmin TSLP, preventing its interaction with TSLP receptor complex. Given the broad mechanism of action, tezepelumab seems to be effective both in Type 2-high and Type 2-low asthma, as opposed to other biologics approved for the treatment of severe asthma, which target specifically Type 2 inflammatory pathways. Indeed, the 2022 GINA guidelines recommended anti-TSLP therapy for patients with severe asthma (step-5) with and without evidence of Type-2 inflammation.[1]

Tezepelumab was approved on the basis of the phase 2b PATHWAY study[12] and the phase 3 NAVIGATOR study.[103] The PATHWAY study evaluated the efficacy of tezepelumab in patients with uncontrolled asthma despite treatment with medium/high dose of ICS/LABA and history of moderate/severe exacerbations. Tezepelumab, tested at different doses, proved to be more effective than placebo to reduce annualized asthma exacerbation rate regardless of BEC (≥250 or <250 cells/μL), FeNO (≥24 ppb or <24 ppb) and Type 2 status (high, with IgE level >100 IU/μL and BEC ≥140 cells/μL or low, with IgE level ≤100 IU/μL or BEC <140 cells /μL). The results showed that tezepelumab effectively lowers asthma exacerbation over 52 weeks by 71% and improved lung function (FEV_1 +130 mL), asthma

control and quality of life compared to placebo. In the NAVIGATOR study on 1061 patients, tezepelumab reduced asthma exacerbation rate (primary outcome) and improved lung function, asthma control and quality of life, irrespective of BEC (including patients with eosinophils <150 cells/μL), FeNO (≥25 ppb or <25 ppb) and sensitization to perennial allergens, even though it was more beneficial for patients with high eosinophils (BEC≥150 cells/μL) and high FeNO levels. In overall population (mean BEC 340 cells/μL) asthma exacerbation rate was 0.93 in the tezepelumab group vs 2.10 in the placebo group with a significant, albeit smaller, reduction in patients with BEC< 150 cells/μL, suggesting a potential effect also in Type 2-low asthma. However, the SOURCE study [104] investigating the efficacy of tezepelumab in sparing steroids in OCS-dependent asthmatics failed the endpoint. Indeed, a significant reduction was observed only in patients with eosinophils ≥150 cells/μL confirming the efficacy in patients with Type 2 asthma and challenging the efficacy of tezepelumab in non-eosinophilic asthma. The issue deserves further investigation, and a possible answer might come from the ongoing studies WAYFINDER [105] and SUNRISE [106] evaluating OCS sparing in severe asthmatic patients.

The long-term safety and sustained efficacy of tezepelumab over 2 years was reported in the DESTINATION trial[107] conducted in 1209 patients who completed the NAVIGATOR or SOURCE studies. Interestingly, once again, a better clinical response in terms of exacerbations was seen in patients with high levels of Type 2 inflammation biomarkers. On the other side, since tezepelumab have been shown to reduce asthma exacerbations and to improve asthma control and lung function even in patients with low eosinophilic inflammation (BEC< 150 cell/ μL), two different studies were designed to elucidate its effect on airway tissue inflammatory cells, remodelling, and airways hyperresponsiveness (AHR). The CASCADE study[108] investigated the effects of tezepelumab on airway inflammatory cells, airway remodelling, and airway hyperresponsiveness. Compared to placebo, treatment with tezepelumab resulted in a significative reduction of the number of eosinophils in bronchial biopsy specimens, although no significant differences have been shown in the other cell types (neutrophils, CD3+ T cells, CD4+ T cells, tryptase-positive mast cells, chymase-positive mast cells), suggesting once again major effects of tezepelumab on eosinophilic inflammation. Moreover, the reduction of eosinophils in subepithelial membrane and in broncho-alveolar lavage (respectively of 74% and 75%) showed in the UPSTREAM study[109] together with a significant reduction of airway tissue mast cells further support a possible role of tezepelumab in Type 2-high inflammation. The role of tezepelumab on AHR remains to be elucidated. In the CASCADE study tezepelumab significantly reduced mannitol induced AHR, while the UPSTREAM study failed to reduce AHR, even if a greater proportion of patients without AHR after 12 weeks was observed in the active group. Moreover, the mannitol induced AHR reduction in the tezepelumab group in the CASCADE study was observed without differences in basement membrane thickness or airway epithelial integrity, suggesting that tezepelumab may exert its effect acting only on the inflammatory component of AHR.[110]

New molecules under investigation

Targeting inflammatory mediators at a higher level could expand the possibility to find biologicals also for severe asthmatic patients with Type 2-low inflammation. An opportunity could have been to develop biologicals targeting upstream alarmins like IL-33, TSLP, and IL-25.[111] Unfortunately, tezepelumab, as it has been shown to be more effective in patients with Type 2-high profile, did not fully meet this need. However, new molecules are under investigation such as monoclonal antibody targeting IL-33 (itepekimab)[112] and the IL- 33 ST2 receptor (astegolimab).[113]

Amlitelimab, a human mAb that binds to the OX40-ligand (OX40L), which is showing benefits in treatment of atopic dermatitis[114], is now under investigation in preliminary studies for severe asthma.[115] OX40 is expressed on regulator and effector T cells promoting Th1 and Th2 pathways. Moreover, new biologic molecules are under investigation to provide long-acting formulations such as depemokimab, an IL-5 monoclonal antibody, which is currently being investigated for the treatment of patients with severe eosinophilic asthma in the SWIFT [116,117] and NIMBLE trials. [118]

	OMALIZUMAB	MEPOLIZUMAB	BENRALIZUMAB	DUPILUMAB	TEZEPELUMAB
Target and mechanism of action	Binds to IgE preventing the binding to IgE receptor on basophils and mast cells and blocking the release of histamine and other inflammatory mediators; moreover, downregulates IgE receptor expression.	Binds to IL-5 preventing the interaction to the receptor and reducing the production and survival of eosinophils.	Binds to IL-5Rα blocking its signaling and the proliferation of IL-5-dependent cell lines.	Binds to IL-4Rα, inhibiting IL-4 and IL-13 signaling preventing eosinophil infiltration into lung tissue, smooth muscle contraction and mucus hypersecretion.	Binds to the alarmin TSLP blocking both the T2 (through both the acquired and innate immunity) and the non-T2 (by inhibiting the differentiation of Th17 cells) inflammatory pathway.
Indications	6 years of age and older Total serum IgE level between 30-1500 IU/mL Evidence of sensitization to a perennial aeroallergen.	6 years of age and older Eosinophilic asthma. *	12 years of age and older Eosinophilic asthma. *	6 years of age and older Eosinophilic asthma; * FeNO > 25 ppb	12 years of age and older
Interval and route of administration	SC injection 75 to 375 mg every 2 to 4 weeks according to body weight and level of serum total IgE.	SC injection Adults (≥12 yrs.): 100 mg every 4 weeks Children (6–11 yrs.): 40 mg every 4.	SC injection 30 mg every 4 weeks for the first 3 doses then every 8 weeks.	SC injection 300 mg every 2 weeks.	SC injection 210 mg every 4 weeks.
Additional licensed indications	Chronic spontaneous urticaria CRwNP	EGPA CRwNP	None	Atopic dermatitis CRwNP Eosinophilic esophagitis	None
Primary outcomes in clinical trials					
• **Exacerbations**	INNOVATE: 26% reduction	MENSA: 52% reduction	SIROCCO: 51% reduction	QUEST: 48 % reduction	NAVIGATOR: 56% reduction
• **Lung function (FEV_1 improvement)**	INNOVATE: +190 ml	MENSA: +98 ml	SIROCCO: +159 ml	QUEST: +340 ml	NAVIGATOR: +230 ml
• **OCS Sparing**	EXALT: 63% of patients reduced/discontinued OCS	SIRIUS: 50% Median reduction of OCS	ZONDA: 52% of patients discontinued OCS (75% median reduction); PONENTE: 82% of patients reduced OCS dosage.	VENTURE: 80% of patients reduced OCS dosage and 48% completely discontinued OCS.	None

*depending on local prescription criteria.

Table 1. Biologic agents approved by food and drug administration for the treatment of severe asthma. FeNO (fractioned exhaled nitric oxide), CRwNP (chronic rhinosinusitis with nasal polyposis), EGPA (eosinophilic granulomatosis with polyangioitis), SC (sub-cutaneous), FEV1 (forced expiratory volume in the first second); OCS (oral corticosteroids)

Choice of monoclonal antibody treatment according to patient characteristics

Even though high-level evidence is lacking to guide the correct choice of a biologic treatment, clinicians have to be guided by some criteria in the process of decision making. The clinical characteristics of patient, such as exacerbations history, OCS use, lung function impairment, poor asthma control, age of onset and comorbidities (phenotype), together with the underlying inflammatory process (endotype) predict the need for biologic therapy.[5]

Therefore, a precise identification of the patient's endo-phenotype is the mandatory step. While in allergic non-eosinophilic severe asthmatics with high levels of blood IgE and a documented positivity to a perennial aeroallergen, omalizumab should be the first option, in patients with severe eosinophilic asthma the choice of biological is more complex as the available molecules target similar Type 2-high inflammatory pathways. [119]

This hypothetical simplified algorithm is shown in Figure 3.

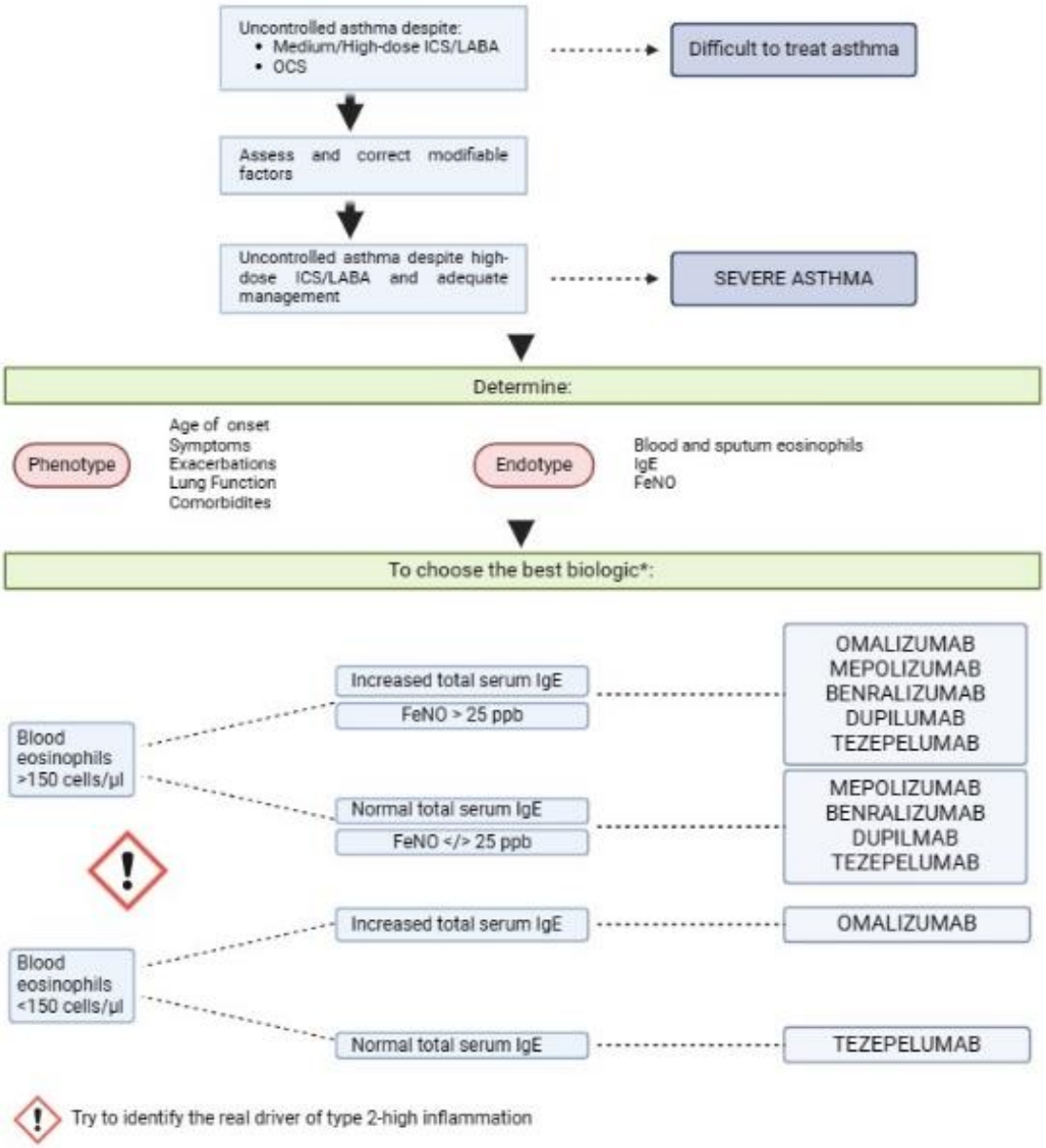

Figure 3. Management of uncontrolled severe asthma and biological treatment options. ICS (inhaled corticosteroid), LABA (long acting β2 agonist), OCS (oral corticosteroids), IgE (immunoglobulin E), FeNO (fractioned exhaled nitric oxide), CRwNP (chronic rhinosinusitis with nasal polyposis, EGPA (eosinophilic granulomatosis with polyangioitis).
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Conclusions and future directions

Asthma is a heterogeneous inflammatory disease, nowadays biologics are available only for Type 2-high severe asthma. Biologics target different mediators and pathways of Type 2-high inflammation that often overlap in defining the clinical phenotype of patient (e.g. eosinophilic/atopic vs eosinophilic/non-atopic) getting difficult to choose "the right biologic for the right patient". Moreover, even if biomarkers are used in clinical practice to prescribe biologics, they are still far to define a unique endo/phenotype to gain a tailored approach. Exploration of the true driver of Type 2-high inflammation together with a well clinical characterization of asthmatic patients will help set the right path for personalized medicine.

Conflicts of interest statement

The authors have no competing interests with any organization or entity with a financial interest in competition with the subject, matter, or materials discussed in the manuscript.

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