Dupilumab and tezepelumab in severe refractory asthma: new opportunities

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Abstract: Bronchial asthma is a chronic inflammatory condition with increasing prevalence worldwide that may present as heterogeneous phenotypes defined by the T2-mediated pattern of airway inflammation T2-high and T2-low asthma. Severe refractory asthma includes a subset of asthmatic patients who fail to control their disease despite maximal therapy and represent a group of patients needing marked resource utilization and hence may be eligible to add-on biological therapies. Among the new biologics, we focused our attention on two monoclonal antibodies: dupilumab, exerting a dual blockade of cytokine (interleukin (IL)-4 and IL-13) signaling; and tezepelumab, acting at a higher level preventing the binding of thymic stromal lymphopoietin (TSLP) to its receptor, thus blocking TSLP, IL-25, and IL-33 signaling, hence modulating airway T2 immune responses. With their different mechanisms of action, these two biologics represent important options to provide an enhanced personalized treatment regimen. Several clinical trials have been conducted testing the efficacy and safety of dupilumab in severe refractory asthmatic patients showing improvements in lung function, asthma control, and reducing exacerbations. Similar results were reported with tezepelumab that, differently from dupilumab, acts irrespectively on eosinophilic or non-eosinophilic phenotype. In this review, we provide an overview of the most important highlights regarding dupilumab and tezepelumab characteristics and mechanism of action with a critical review of the principal results of clinical (Phase II and III) studies concluded and those still in progress.

Keywords: biologic therapies, dupilumab, severe refractory asthma, T2 inflammation, tezepelumab

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Introduction

Bronchial asthma is a chronic disease of the airways characterized by reversible airflow obstruction, bronchial hyperresponsiveness, airway inflammation, and recurrent flare-ups.1 The prevalence of the disease has been increasing in the 20th century with an estimated 300 million people worldwide having the condition.2

Asthma includes several distinct endotypes which represent different pathways of the immune and inflammatory response. T lymphocytes, both CD4 and CD8, can be divided into T1 and T2 subsets according to their functions and the cytokines produced. Most asthmatic patients, about 50–70%, present with T2 inflammation characterized by increased interleukin (IL)-4, IL-5, and IL-13, and a prevalent eosinophilic inflammation in the airways,3 usually associated with blood eosinophilia.

Eosinophilia in patients with asthma may reflect airway inflammation and may be detected on induced sputum, though fractional exhaled nitric oxide (FeNO) is another biomarker of T2 inflammation which mildly correlates with sputum and blood eosinophils.4 This aids in the assessment and management of severe asthma, and to predict
the responsiveness to biological therapies. Elevated IgE levels and atopic status are also features of T2 inflammation; however, eosinophilic and T2 inflammation, in general, can be present in non-atopic asthmatic subjects.

There is an increased risk for patients with uncontrolled persistent asthma of severe exacerbations, hospitalization, morbidity, and mortality. In addition, the oral corticosteroids (OCSs) prescribed to these patients frequently are associated with substantial short- and long-term side effects with a high cost of managing OCS morbidity.

A great effort was made in the last decades to assess different inflammatory pathways and to identify possible therapeutic targets. Suggestive studies hypothesized a potential role of potassium channel modulators to control airway hyperresponsiveness, reduce airway remodeling, or having an antisecretive role. Several biologics have been developed which are able to attenuate or abolish specific inflammatory pathways, with the aim of providing enhanced personalized asthma treatment.

Currently (though not all licensed), available biologics for patients with severe uncontrolled asthma include inhibition of immunoglobulin (Ig)-E, IL-4, IL-5, IL-13, and thymic stromal lymphopoietin (TSLP), directly or through their respective receptors. Anti-IgE and anti-IL-5 are the first biologics approved for severe asthmatic patients, and a great amount of studies have been provided showing their efficacy. A subgroup of asthmatic patients present with a neutrophilic or a paucigranulocytic inflammatory pattern, and to date, efforts made to identify a therapeutic target for these patients have been unsuccessful.

Here we focus our attention on two more recent biological therapies developed for severe refractory asthma being investigated or under licensing application, namely dupilumab, an IL-4 receptor (R) alpha antagonist, and tezepelumab, a monoclonal antibody that binds to TSLP. We conducted literature searches on PubMed, MEDLINE, and international conferences, presentations/abstracts for ‘dupilumab AND/OR tezepelumab, AND asthma as keywords. English papers only were considered. Ongoing trials were searched on ClinicalTrials.gov with the same keywords. The aim of this narrative review is to describe the most important highlights, in terms of their mechanism of action, pharmacokinetics (PKs), and clinical studies conducted to date.

**Mechanism of action, pharmaco-kinetics, and -dynamics**

**Dupilumab**

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signaling through its binding to the shared IL-4R alpha (α) subunit. IL-4 and IL-13 signaling is vital in Th2 asthma pathogenesis; IL-4R is expressed by Th2 cells, mast cells, basophils, group 2 innate lymphoid cells (ILCs) 2, and B cells. There are two different IL-4R forms, type I and II and they share a common subunit, IL4R-α. Type I receptor binds IL-4 only, whereas the type II receptor consists also of IL13R1-α, hence binding both IL-13 and IL-4. Dupilumab is able to bind both IL-4 receptor types inhibiting their signaling.

The *primum movens* of Th2 inflammatory pattern activation is the airway epithelial cells’ exposure to allergen which initiates synthesis and release of IL-25, IL-33, and TSLP. These substances stimulate dendritic cell expression of IL-4, CCL17, and CCL22 causing polarization of Th0 in Th2 lineage and start eosinophil enrollment by activating ILC2. Hence, there is a profound IL-4 release, which is the leading actor in Th2 inflammation.

Th2 cells release IL-4 (amplifying its action), IL-5, IL-9, and IL-13. The former and latter induce IgE production promoting B cells’ class switching. Concurrently, basophils, mast cells, ILC2, alveolar macrophages, and eosinophils secrete IL-4 in the airways.

Protracting of this inflammatory mechanism has several consequences on airways structure, and function, inducing ongoing damage and remodeling. Notably, IL-13 induces basement-membrane thickening by collagen deposition in the epithelium and hyperplasia, and hypertrophy of the airway smooth muscle. In addition, IL-13 has been possibly implicated in the process of neo-angiogenesis and increased airway mucus secretion. IL-4 and IL-13’s pathways and dupilumab’s action are shown in Figure 1.
Figure 1. Dupilumab and tezepelumab’s mechanisms and pathways. Dupilumab exerts a dual blockade of IL-4 and IL-13 signaling inducing beneficial effects in T2 phenotypes. Tezepelumab prevents binding of TSLP to its receptor blocking TSLP, IL-25, and IL-33 signaling. Acting in an upstream position in the airway inflammatory cascade, it is suitable for regulating both the Th1 and Th2 immune responses.

Abbreviations: TSLP: thymic stromal lymphopoietin; IL: interleukin; ILC2: group 2 innate lymphoid cells; Th: T helper lymphocytes.
Several studies demonstrated better outcomes and significant improvement of pulmonary function using dupilumab in patients with severe asthma.18,19

Dupilumab is primarily distributed in the vascular system where it is degraded into small peptides and individual amino acids and has non-linear clearance.20 Recently, Zhang et al.21 developed the first Population Pharmacokinetic (PopPK) model for adult and adolescents patients with asthma. This establishes that dupilumab’s PK properties are similar in patients with asthma and atopic dermatitis, compared to the healthy population. They examined several patient characteristics and observed that only body weight influenced the PK, though dose adjustment of dupilumab depending on weight is not currently suggested.

**Tezepelumab**

Tezepelumab is a humanized monoclonal antibody, which prevents binding of TSLP to its receptor.22,23 TSLP, a cytokine belonging to the group of ‘alarmins’, is a pleiotropic cytokine that is mainly synthesized and released from keratinocytes, airway, and gut epithelial cells in response to inflammatory triggers.23 It is pivotal to the activation and regulation of type 2 immunity.20,22 TSLP binding to its receptor results in the formation of a heterodimer with IL-7 receptor-α (IL7Rα), leading to activation of Janus kinase (JAK)-signal transducer and activator of transcription protein (STAT) intracellular pro-inflammatory signaling.22,23 The intracellular signaling network activates genes encoding Th2 cytokines, such as IL-4, IL-5, IL-9, and IL-13.22,24 Furthermore, TSLP acts on dendritic cells, B and T lymphocytes, innate immune cells, and eosinophils, in particular, promoting eosinophil viability inhibiting processes of apoptosis and inducing production of IL-6, eosinophil-derived neurotoxin, and chemokines.23 Moreover, TSLP plays a role in promoting eosinophil transmigration and tissue accumulation acting on the regulation of ICAM1, CD18, and L-selectin surface expression.25

Due to its upstream position, TSLP plays a pivotal role in the airway inflammatory cascade, which characterizes the pathophysiology of asthma, by regulating both the Th1 and the Th2 pathway.26,27 TSLP, IL-25, and IL-33 released from airway epithelial cells activate ILC2,15 which are increased in the airways of severe asthmatic patients,26 enhancing ILC2-mediated immune responses and glucocorticoid resistance.22 Activation of the receptor also causes dendritic cell polarization and stimulation of various immune cell types, including type 2 helper T cells (Th2), basophils, mast cells, and eosinophils, thus promoting airway Th2 immune responses.22,23 Figure 1 depicts the mechanism of tezepelumab’s action.

The PATH-BRIDGE (NCT03989544), a Phase I study, evaluated the PKs of 210 mg tezepelumab delivered subcutaneously (sc) with pre-filled syringe or autoinjector (AI) versus vial and syringe in healthy individuals.29 There were no differences among the three drug administration strategies with regard to the PKs, immunogenicity, injection-site issues, and reported side effects, hence making it suitable for at-home autoinjecting of tezepelumab.

**Review of clinical (phase II and III) studies using dupilumab/tezepelumab**

Several studies about efficacy and safety of dupilumab and tezepelumab in patients with severe asthma have been conducted while others are still in progress. Here we describe and summarize the phase II and III studies in both biologics.

**Dupilumab studies**

The first phase II double-blind, placebo-controlled (DBPC), randomized parallel-group study (NCT01312961) on the efficacy and safety of dupilumab was conducted in 104 adult patients with moderate-to-severe persistent asthma, not well controlled with medium-to-high dose ICS and long-acting β2 agonists (LABA), with >300 blood eosinophils/µl or >3% sputum eosinophils.30 Patients were randomized 1:1 to receive subcutaneously 300 mg of dupilumab or placebo once weekly for 12 weeks. The LABA was ceased at week 4, while the ICS at weeks 6–9. It was reported that compared to patients on placebo, those treated with dupilumab had significantly lower asthma exacerbations. Secondary outcome was significant reductions in time to asthma exacerbations and risk of exacerbations, improvements in FEV1 and reduction in ACQs scores. In addition, T2 biomarkers, such as FeNO, eotaxin,
thymus, and activation-regulated chemokine (TARC), IgE, all decreased at the end of the study in actively treated patients. Of note, in the dupilumab-treated patients, the decrease in FeNO correlated with an increase in FEV1, though no decrease in blood eosinophils was reported. Importantly, no difference in adverse events were reported between the two treatment groups.

In 2016, Wenzel et al.\textsuperscript{31} published another phase II study (NCT01854047) assessing the efficacy and safety of dupilumab; 769 patients with uncontrolled persistent asthma were randomized in a DBPC study to receive dupilumab at doses of 200 or 300 mg every 2 or 4 weeks for 24 weeks, as add-on therapy to ICS/LABA, compared to placebo (1:1:1:1:1). Unlike the previous phase II study,\textsuperscript{30} the patients’ controller therapy was maintained for the entire study duration and the primary endpoint in the intention-to-treat (ITT) population was the difference in FEV1 in patients with a baseline eosinophil count of 300/μl. Subjects were recruited independently from baseline blood eosinophils and irrespective of the dupilumab dose administered, significant improvements in lung function and in annualized rates of exacerbations compared to placebo were reported, though the greatest increases were in the 200 and 300 mg dupilumab-treated groups on a two weekly basis in patients with >300 eosinophils/μl at baseline. Similar observations were made in the patients with less than 300 eosinophils/μl at baseline. There were no safety concerns with dupilumab administration, though the study was underpowered to establish the more efficacious dose and frequency.

In a phase III (LIBERTY—ASTHMA QUEST; NCT02414854) optimal dupilumab dose identifying study (200 and 300 mg, every 2 weeks for 52 weeks) besides safety and efficacy compared to placebo was conducted on patients ≥12 years of age with uncontrolled moderate-to-severe asthma irrespective of their baseline blood eosinophil count.\textsuperscript{32} A total of 1902 patients were recruited with the co-primary endpoint of the study being annualized severe asthma exacerbation rates and the change in pre-bronchodilator FEV1 at 12 weeks. Bi-weekly dupilumab at both doses were noted to markedly attenuate the annualized asthma exacerbation rates, emergency department attendance, or hospitalizations. Moreover, there were significant improvements in FEV1 with the lower dupilumab dose (320 ml) compared to placebo (140 ml). Of note, patients with eosinophil counts >150/μl had reductions in the annualized exacerbation rates with both dupilumab doses compared to placebo, though this was more pronounced in patients with a baseline eosinophil count of >300/μl. Sub-analyses of the randomized patients reported that the benefits of dupilumab were greater in patients with a FeNO of ≥25 ppb greater, the improvements in the FEV1 were evident within 2 weeks and maintained throughout the study in patients with eosinophilia and elevated FeNO levels. T2 biomarkers (FeNO, total IgE, periostin, eotaxin-3, and TARC) decreased with dupilumab treatment compared to placebo; however, an increase in blood eosinophils was noted in more patients on dupilumab (4.1%) compared to placebo (0.6%). Of note, the presence of antibodies toward dupilumab was low and did not affect its efficacy. A post hoc analyses of the index study also reported improvements in the post-bronchodilator FEV1 and subjective asthma control assessments.\textsuperscript{33}

The VENTURE study, another phase III study (NCT02528214) evaluated the prospect of attenuating the use of OCS with 300 mg of dupilumab every 2 weeks for 24 weeks in 202 corticosteroid-dependent severe asthmatic patients compared to placebo.\textsuperscript{34} During the study, OCS were decreased from week 4 to 20 and then maintained till the end of the study. The primary outcome, which was the reduction in corticosteroid use, was significant in dupilumab-treated patients compared with placebo. Despite this OCS reduction, exacerbation rates were reduced and FEV1 increased in dupilumab-treated patients. Akin to earlier studies, a higher percentage of dupilumab-treated patients experienced a transient increase in blood eosinophils (14%).\textsuperscript{31,32} Although, patients were not recruited based on the baseline blood eosinophil levels, the effect of dupilumab in reducing the corticosteroid use was more evident in subjects with higher baseline eosinophils. The FeNO levels decreased in the dupilumab-treated patients from week 2 for the duration of the study.

In children with severe asthma and those having recurrent asthma exacerbations, T2 inflammation is commonly observed, and a post hoc analysis of the LIBERTY ASTHMA QUEST study suggested that biologics assessed in adults may be efficacious.\textsuperscript{35} On this premise, a DBPC RCT
(NCT02948959) was conducted in 6- to 11-year-olds with uncontrolled moderate-to-severe asthma to receive sc dupilumab (depending on their weight) or placebo weekly for 52 weeks. The two primary efficacy cohorts included a T2 inflammation of ≥150 eosinophils/µl or a FeNO of ≥20 ppb, or an eosinophil count of >300/µl. In the former efficacy population assessed, the primary endpoint, annualized asthma exacerbation rate, significantly attenuated with associated improvements in subjective asthma control and lung function in favor of children treated with add-on dupilumab compared to placebo. Similar significant dupilumab beneficial improvements were noted in children with an eosinophil count of >300/µl. The safety of dupilumab was similar to that of placebo in the study.

More recently, an open-labeled extension phase III study to establish the long-term efficacy and safety of dupilumab treatment in patients with moderate-to-severe asthma (TRAVERSE; NCT02134028) has been conducted with the primary endpoint being the number and percentage of patients with any treatment-related adverse events. Patients (n = 2282) from the earlier conducted phase II and III studies (EXPEDITION; DRI, QUEST or VENTURE) were enrolled to receive 300 mg of dupilumab every 2 weeks for up to 96 weeks. The safety of dupilumab was noted to be similar to the shorter primary studies, with only four treatment-emergent deaths. All secondary efficacy outcomes in the TRAVERSE study were reached akin to the prior parent studies, including reduction in annualized asthma exacerbation rate, rapid and sustained improvements in pre-bronchodilator FEV1, asthma control, and asthma-related quality of life. Importantly, these outcome parameters were also observed in patients who were on the placebo arm of the primary studies. During the study, it was observed that the blood eosinophils and total IgE levels progressively declined with dupilumab treatment. In the subgroup of patients with T2 high biomarkers at 148 weeks follow-up, the exacerbation rates continued to decline with maintained lung function improvements.

In a phase II study (NCT03387852) to evaluate a new biological agent compared to placebo in patients with severe asthma, itepekimab (an IL-33 antagonist), out of the three treatment arms one was randomized to itepekimab 300 mg monotherapy and two arms had dupilumab 300 mg every 2 weeks for 12 weeks; one arm in combination with itepekimab and in another alone. Similar to the study by Wenzel et al., LABA cessation and ICS tapering were performed. In all three active treatment groups, there was better asthma control, and in both monotherapy groups, improvements in pre-bronchodilator FEV1 compared to placebo. Importantly, there were comparable adverse events in all four trial groups. All patients on active treatment reported a reduction in T2 biomarkers, apart from blood eosinophils for dupilumab.

In a retrospective French multicenter study to evaluate the changes in asthma control with 12-month treatment with dupilumab in patients (n = 64) with severe asthma experiencing corticosteroid-related adverse events and/or severe asthma exacerbations, it was reported that asthma control improved significantly from baseline. These improvements were in association with enhanced lung function, reductions in annualized asthma exacerbations, and also reductions in the daily oral corticosteroid doses. Although eosinophilia was noted in a quarter of the patients enrolled and in just over half (n = 8) them persisting for over 6 months, there were clinical response modifications over the period of assessment.

**Dupilumab ongoing studies**

There are numerous clinical trials underway using dupilumab assessing its safety, efficacy, changes in physiological parameters and also in combination with other biologic therapy in patients with moderate-to-severe asthma. These have been summarized in Table 1.

**Tezepelumab studies**

A 52-week, Phase II (PATHWAY; NCT02054130), dose-finding study in 584 patients with moderate-to-severe uncontrolled asthma on medium-to-high dose ICS and LABA was randomized in a DBPC fashion to receive sc tezepelumab at doses of 70 or 210 mg every 4 weeks, 280 mg every 2 weeks, or placebo for 52 weeks. The annualized rate of asthma exacerbations, the primary endpoint, decreased significantly by 62%, 71%, and 66%, respectively, compared with placebo, irrespective of the baseline peripheral blood eosinophil cell count. In
Table 1. Characteristics of clinical trials of dupilumab in patients with severe asthma.

| Studies                        | Drugs            | Ref        | Population                                                                 | n    | Design     | Dose                           | Phase   | Follow-up                                                                 | Primary outcome                                                                                     | Results                                                                                       |
|--------------------------------|------------------|------------|----------------------------------------------------------------------------|------|------------|--------------------------------|---------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Published studies              |                  |            |                                                                            |      |            |                                |         |                                                                            |                                                                                                |                                                                                                |
| NCT01312961, Wenzel et al.     | Dupilumab versus placebo | 30         | Adults with persistent moderate-to-severe eosinophilic asthma in therapy with ICS + LABA | 104  | RCT        | QW (once weekly)              | II      | 12-week treatment + six to eight follow-ups                                 | Percentage of asthma exacerbation                                                                  | Reduction of exacerbation, improved lung function, and reduction of markers related to Th2 inflammation |
| NCT01854047, Wenzel et al.     | Dupilumab 300 mg Q2 W versus dupilumab 200 mg Q2 W versus dupilumab 300 mg Q4 W versus dupilumab 200 mg Q4 W versus placebo Q2W | 31         | Adults with severe asthma                                                    | 769  | RCT        | Two doses on day 1 followed by one injection every 2 or 4 weeks            | II      | 24-week treatment + 16-week follow-up                                       | Change from baseline of FEV1                                                                       | Increased lung function and reduced exacerbations in patients treated with dupilumab              |
| LIBERTY ASTHMA QUEST NCT0244854, Castro et al. | Dupilumab 200 mg/dose versus dupilumab 300 mg/dose versus placebo | 32         | Adults and adolescents with uncontrolled asthma                             | 1902 | RCT        | Two doses on day 1 followed by Q2W randomized in 200 or 300 mg/dose       | III     | 52-week treatment + 12-week follow-up                                       | Annualized rate of severe exacerbation events. Changes in FEV1 pre-bronchodilator (BD)           | Lower rate of exacerbations in patients treated with dupilumab than placebo                      |
| VENTURE NCT02528214 Rabe et al. | Dupilumab versus placebo | 34         | Adults and adolescents with severe steroid-dependent asthma                 | 210  | RCT        | Q2W                            | III     | 24-week treatment                                                          | Efficacy for reducing the use of maintenance OCS                                                  | Dupilumab treatment reduced use of OCS while decreasing the rate of severe exacerbations and increasing the FEV1 |
| NCT02948959, Bacharier et al.  | Dupilumab versus placebo | 36         | Children between the ages of 6 and 11 years who had uncontrolled moderate-to-severe asthma | 408  | RCT        | 100 mg for subjects weighing <30 kg and 200 mg for those weighing >30 kg | III     | 52-week treatment                                                          | Annualized rate of severe asthma exacerbations (AAR)                                            | Lower rate of exacerbations in patients treated with dupilumab                                  |
| NCT03387852, Wechsler et al.   | 9ARA403040/REGN3500 Monotherapy sc versus dupilumab versus 9ARA403040/REGN3500 + dupilumab versus placebo | 38         | Adults with moderate-to-severe asthma in therapy with ICS + LABA             | 296  | RCT        | Q2W                            | II      | 12 weeks for the first treatment + 12 weeks for the second treatment       | Proportion of patient with LOAC                                                                   | Lower incidence in patients treated with itepekimab than placebo                                |
| NCT04022247, Duquin et al.     | Dupilumab         | 39         | Uncontrolled SA with no available treatment option left                      | 64   | Retrospective real-life cohort study                                        | Q2W     | -                              | 48 weeks                                                      | Asthma control                                                                                  | Dupilumab significantly improved asthma control and lung function and reduced oral steroids use and exacerbations rate |

Post hoc studies

| Castro et al.                  | Dupilumab 200 mg/dose versus dupilumab 300 mg/dose versus placebo | 33         | Uncontrolled, moderate-to-severe                                          | 1902 | RCT        | Two doses on day 1 followed by Q2W randomized in 200 or 300 mg/dose      | III     | 52 weeks                                                                  | Effect on lung function in the overall population, and subgroups with baseline elevated type-2 inflammatory biomarkers | Lung function improvement, particularly in subjects with T2 inflammation                           |
| Maspero et al.                 | Dupilumab 200 versus dupilumab 300 mg/dose versus placebo         | 35         | Adolescents with uncontrolled, moderate-to-severe                          | 107  | RCT        | Two doses on day 1 followed by Q2W randomized in 200 or 300 mg/dose      | III     | 52 weeks                                                                  | Efficacy of dupilumab in subgroup of adolescents                                                | Improved lung function and reduced levels of type-2 biomarkers adolescents with uncontrolled, moderate-to-severe asthma |

(Continued)
| Studies          | Drugs                          | Ref                          | Population                      | n    | Design  | Dose                          | Phase | Follow-up                  | Primary outcome                                                                 | Results                                                                 |
|------------------|-------------------------------|------------------------------|--------------------------------|------|---------|-------------------------------|-------|----------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| NCT03112577      | REGN3500 (itepekimab) ev versus dupilumab sc versus REGN3500 ev + dupilumab sc versus placebo |                              | Adults with mild allergic asthma | 32   | RCT     | 1                            | 1     | 42 weeks                   | Difference in BAC-induced changes in spumtum inflammatory markers in individuals treated with REGN3500, dupilumab and the combination of REGN3500 plus dupilumab or placebo |                                                                                |
| EXPEDITION, NCT0397333 | Dupilumab versus placebo        |                              | Adults with severe asthma     | 42   | RCT     | Two doses on day 1 followed by Q2W | II    | 12-week treatment + 12-week follow-up | Effects on airway inflammation                                                   |                                                                                |
| NCT03782532      | Dupilumab versus placebo        |                              | Adults and adolescents with severe asthma | 484  | RCT     | Q2W                           | III   | 24-week treatment + 12-week follow-up | Changes in FEV1 pre-bronchodilator                                          |                                                                                |
| NCT03620747      | Dupilumab                      |                              | Patients who completed the treatment period in the clinical study LST12551 (TRAVERSE) | 750  | Open-label intervention         | Q2W                           | III   | 3 years                    | Long-term safety in patients treated with dupilumab (TEAE)                      |                                                                                |
| NCT03884842      | Dupilumab versus placebo        |                              | Adults and adolescents with severe asthma | Recruiting estimated 32 | RCT     | Two doses on day 1 followed by Q2W | III   | 16 weeks                   | At least one doubling dose improvement in PC20 methacholine and a 50% reduction in post-BD FEV1 |                                                                                |
| NCT05097287      | Dupilumab versus placebo        |                              | Adults and adolescents with severe asthma | Recruiting estimated 1828 | RCT     | Two doses on day 1 followed by Q2W | IV    | 3-year treatment + 12-week follow-up | Changes in post-BD FEV1                                                        |                                                                                |
| IDEA NCT03694158, Phipatanakul et al. | Dupilumab versus placebo        |                              | Adults and adolescents with severe asthma, carrying the IL-4R576 gene variant | Recruiting estimated 150 | RCT     | Two doses on day 1 followed by Q2W | IV    | 48-week treatment          | Rate of asthma exacerbations                                                   |                                                                                |
| NCT04203799      | Dupilumab versus placebo        |                              | Adults with severe asthma      | Recruiting estimated 140 | RCT     | Two doses on day 1 followed by Q2W | IV    | 12 weeks                   | Improving exercise capacity in patients with severe asthma                    |                                                                                |
| VESTIGE NCT04400318 | Dupilumab versus placebo        |                              | Adults and adolescents with severe asthma | Recruiting estimated 153 | RCT     | Two doses on day 1 followed by Q2W | IV    | 24-week treatment + 12-week follow-up | Changes in post-BD FEV1 and TLC                                               |                                                                                |
| NCT05036733      | Dupilumab                      |                              | Adults and adolescents with severe asthma | Recruiting estimated 15 | Single-group assignment         | Two doses on day 1 followed by Q2W | IV    | 16 weeks                   | Effects on dupilumab on respiratory microbiota                                 |                                                                                |
| NCT04442526      | Dupilumab                      |                              | AERD-Aspirin-e acerated respiratory disease | Recruiting estimated 30 | Single-group assignment, open label | Q2W                           | IV    | 6 months                   | Maximally tolerated aspirin dose level                                            |                                                                                |
| NCT04998604      | Dupilumab versus omalizumab versus placebo |                              | Adults with bilateral sino-nasal polyposis and asthma | Recruiting estimated 422 | RCT     | Q2W                           | IV    | 4-week screening + 24-week intervention + 12-week follow-up | Changes in nasal polyp score, changes in University of Pennsylvania Sino Identification Test |                                                                                |
| MDR-HED NCT04502862 | Dupilumab versus placebo        |                              | Adults and adolescents with severe asthma | Recruiting estimated 260 | RCT     | Two doses on day 1 followed by Q2W | IV    | 12-week treatment + 12-week follow-up | Change in sleep disturbance score in Asthma Sleep Disturbance Questionnaire |                                                                                |
| NCT04743791, Sally et al. | Dupilumab versus placebo        |                              | Adults with severe asthma       | Recruiting estimated 30 | RCT     | Two doses on day 1 followed by Q2W | IV    | 12 weeks                   | Change in mucociliary clearance (MCC) rate                                      |                                                                                |

Table 1. (Continued)
addition, the pre-bronchodilator FEV1 at the end of the study period showed significant increases in >120 ml in all three tezepelumab doses compared to those on placebo. There was similar overall incidence of adverse events in all the study groups. Importantly, marked and sustained in blood eosinophils and FeNO levels, and progressive decline in total IgE levels were observed in all the active treatment groups.

A 28-week, phase II DBPC exploratory study (CASACADE;NCT03688074) involving 116 subjects with moderate-to-severe uncontrolled asthma was conducted to assess the effects of 210 mg of sc tezepelumab (n=48) administered four-weekly on airway inflammation, as reflected by the number of inflammatory cells in bronchoscopic biopsy samples (primary outcome), airway remodeling, and airway hyperresponsiveness (AHR). Compared with placebo (n=51), tezepelumab significantly reduced the number of airway sub-mucosal eosinophils ratio of geometric least-squares means [0.15 (95% CI, 0.05–0.41); nominal \( p < 0.001 \)], but not neutrophils, CD3+ and CD4+ T-cells, and tryptase+ and chymase+ mast cells. Subgroup analyses based on T2 inflammatory biomarkers at baseline, including blood eosinophil count, showed no differences. Between-group airway remodeling outcomes, reticular basement-membrane thickness, and epithelial integrity were similar, whereas the reduction of AHR to mannitol was significantly greater in the tezepelumab group. Adverse events were similar across both groups.\(^{40}\) In another smaller phase II bronchoscopic DBPC study (UPSTREAM; NCT02698501), 12-week administration of 700 mg of tezepelumab (n=20) or placebo (20) resulted in similar observations of marked AHR improvements and decline in BAL and airway mucosal eosinophilic inflammation.\(^{41}\)

An open-labeled randomized parallel-group phase III (PATH-HOME;NCT03968978) study was designed to assess the sc administration tezepelumab, on a four-weekly basis in 216 patients with uncontrolled asthma despite being on medium-to-high inhaled corticosteroids and an additional controller therapy, in the clinic and at home in terms of functionality and performance by an accessorized pre-filled syringe (APFS)(n=111) and AI(n=105).\(^{42}\) In this 24-week study, the first, second, third, and sixth administrations were conducted in the clinic by a healthcare professional and the others by the patients or caregivers in the community. It was demonstrated that tezepelumab was equally successfully administered in the clinic or at home with strategies, with clinical subjective improvements and safety, and at-par PKs between the two groups.

The NAVIGATOR (NCT 03347279) study is the largest (n=1061) phase III study to date assessing the efficacy and safety of tezepelumab administered sc at 210 mg four-weekly compared to placebo for 52 weeks in moderate-to-severe uncontrolled asthma.\(^{27}\) Annualized asthma exacerbations were the primary outcome, and this was also assessed in patients with a baseline eosinophil count of <300/µl, besides other secondary endpoints. In patients administered with tezepelumab (0.93), compared to placebo (2.1), the annualized asthma exacerbation rates decreased significantly [rate ratio (RR) 0.44, \( p < 0.001 \)]; similar improvements in the cohort of patients with <300 eosinophils/µl were noted in favor of tezepelumab (1.02; placebo 1.73; RR 0.59, \( p < 0.001 \)). Also, significant improvements in pre-bronchodilator FEV1 and subjective assessments (ACQ-6 scores, AQLQ, and ASD) were noted; though the latter were not clinically significant. Overall, the adverse events were similar in both groups during the study period.

Multiple post hoc analyses have been conducted from the PATHWAY (NCT02054130) study.\(^{26}\) Pham et al.\(^{43}\) have reported that compared to baseline serum Il-5 and IL-13 levels, treatment with tezepelumab resulted in normalization of the levels of both T2 cytokines. In further post hoc evaluations it has been suggested that there is potential clinical efficacy and short-term tolerability of tezepelumab in patients with uncontrolled moderate-to-severe asthma with associated seasonal\(^{14}\) or perennial atopy,\(^{45}\) or nasal polyposis.\(^{46}\)

**Tezepelumab ongoing studies**

There are numerous clinical trials in patients with moderate-to-severe asthma underway using tezepelumab assessing its PKs in different populations, safety, and efficacy in OCS-dependent patient with asthma and specific populations and interaction with the influenza vaccination. These have been summarized in Table 2.
Table 2. Characteristics of clinical trials of tezepelumab in patients with severe asthma.

| Studies | Drugs | Ref | Population | n | Design | Dose | Phase | Follow-up | Primary outcome | Results |
|---------|-------|-----|------------|---|--------|------|-------|-----------|-----------------|---------|
| **Published studies** | | | | | | | | | | |
| PATH-BRIDGE | Tezepelumab (V-S) versus tezepelumab (APFS) versus tezepelumab (AI) | Zheng et al. | Healthy volunteers aged 18–65 years | 315 | Open-label randomized | Single dose | I | 113 days | Comparison of PK parameters between groups | PK parameters were comparable |
| PATHWAY | Tezepelumab 70 mg Q4W versus tezepelumab 210 mg Q4W versus tezepelumab 280 mg Q2W versus placebo | Corren et al. | Adults and adolescents with severe asthma | 584 | RCT | Q4W | IIb | 52 weeks | AAER | Lower annualized rates of asthma exacerbations than the rate with placebo |
| CASACADE | Tezepelumab versus placebo | Diver et al. and Emson et al. | Adults with severe asthma | 116 | RCT | Q4W | II | 28-week treatment + 12-week follow-up | The change from baseline in number of airway submucosal inflammatory cells/mm² of bronchoscopic biopsies | |
| UPSTREAM | Tezepelumab versus placebo | Sverrill et al. | Adults with asthma and AHR to mannitol | 40 | RCT | Q4W | II | 12 weeks | Changes in AHR to mannitol | Reduced AHR |
| PATH-HOME | Tezepelumab (APFS) versus tezepelumab (AI) | Corren et al. | Adults and adolescents with severe asthma | 216 | Open-label randomized | Single dose | III | 24-week treatment + 12-week follow-up | Proportions of HCPs and subjects/caregivers who successfully administered tezepelumab in clinic or at home by device type** | The results of this study support the use of an APFS or AI both at home and in the clinic |
| NAVIGATOR | Tezepelumab versus placebo | Menzies-Gow et al. | Adults with asthma and AHR to mannitol | 1061 | RCT | Q4W | III | 52-week treatment + 12-week follow-up | AAER | Fewer exacerbations, better lung function, asthma control, and health-related quality of life than those who received placebo |
| **Post hoc studies** | | | | | | | | | | |
| Pham et al. | Tezepelumab 70 mg Q4W versus tezepelumab 210 mg Q4W versus tezepelumab 280 mg Q2W versus placebo | Corren et al. | Adults and adolescents with severe asthma | 550 | RCT | Q4W | IIb | 52 weeks | Determine serum IL-5 and IL-13 levels in PATHWAY participants | IL-5 and IL-13 levels were higher in patients with severe asthma. After 52-week tezepelumab treatment, IL-5 and IL-13 in patients with severe asthma |
| Corren et al. | Tezepelumab 70 mg Q4W versus tezepelumab 210 mg Q4W versus tezepelumab 280 mg Q2W versus placebo | Corren et al. | Adults and adolescents with severe asthma | 550 | RCT | Q4W | IIb | 52 weeks | Tezepelumab treatment reduced numbers of AAER across all seasons | Tezepelumab treatment reduced the AAER versus placebo by 66–78% in patients with perennial allergy |
| Emson et al. | Tezepelumab 210 mg versus placebo | Emson et al. | Adults and adolescents with severe asthma with and without nasal polyposis | 550 | RCT | Q4W | IIb | 52 weeks | AAER Change in eosinophil blood count, FeNO, serum levels of IL-5 and IL-13 in patients with or without nasal polyposis | Higher-level blood eosinophil count, FeNO, IL-5 and IL-13 in patients with nasal polyposis. Tezepelumab reduced AAER, FeNO, serum levels of IL-5 and IL-13, eosinophil blood count in both groups |

(Continued)
### Table 2. (Continued)

| Studies          | Drugs                        | Ref                        | Population                  | n  | Design   | Dose         | Phase   | Follow-up | Primary outcome                                                                 | Results                                                                 |
|------------------|------------------------------|----------------------------|-----------------------------|----|----------|--------------|---------|-----------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Ongoing studies  | Tezepelumab low dose         |                            | Healthy subject             | 48 | RCT      | Single dose  | I       | 28 days   | Evaluate the pharmacokinetics, safety, tolerability, and immunogenicity       |                                                                         |
|                  | versus tezepelumab medium    |                            |                             |    |          |              |         |           |                                                                                 |                                                                         |
|                  | dose versus tezepelumab      |                            |                             |    |          |              |         |           |                                                                                 |                                                                         |
|                  | high dose versus placebo     |                            |                             |    |          |              |         |           |                                                                                 |                                                                         |
|                  | NCT04473430                  | Tezepelumab                | Children (5–11 years) with asthma | 14 | Open label | Single dose  | I       | 85 days   | Pharmacokinetic of tezepelumab in children                                      |                                                                         |
|                  | SOURCE                       | Tezepelumab versus placebo | Adults with OCS-dependent Asthma | 150 | RCT      | Q4W          | III     | 48-week treatment and reduction OCS + 12-week follow-up | Categorized percent reduction from baseline in the daily OCS dose while not losing asthma control |                                                                         |
|                  | NCT03927157, Zhong et al.    |                            |                             |    |          |              |         |           |                                                                                 |                                                                         |
|                  | Tezepelumab versus placebo   | Adults and adolescents     | Recruiting estimated       | 356| RCT      | Q4W          | III     | 52-week treatment + 12-week follow-up | AAER                                                                   |                                                                         |
|                  | Adults with severe asthma    |                             |                             |    |          |              |         |           |                                                                                 |                                                                         |
|                  | SOURCE                       | Tezepelumab                | Adults and adolescents with severe asthma | 65 | Open-label | Q4W          | III     | 52-week treatment + 12-week follow-up | Number of subjects with adverse events                                   |                                                                         |
|                  | NCT04049463, Shinkai et al.  |                            |                             |    |          |              |         |           |                                                                                 |                                                                         |
|                  | Tezepelumab versus placebo   | Patients who complete the S2- and 48-week NAVIGATOR and SOURCE studies, respectively. Patient who received Tezepelumab will continue it for 52 weeks, patients who had placebo will be randomized | 951| RCT      | Q4W          | III     | Long-term extension of NAVIGATOR and SOURCE 52 weeks | Exposure adjusted incidence rates of AEs/SAEs, long-term safety and tolerability of tezepelumab over 104 weeks |                                                                         |
|                  | DESTINATION                  | Tezepelumab versus placebo |                              |    |          |              |         |           |                                                                                 |                                                                         |
|                  | NCT03706709, Menzies-Gow et al. |              |                              |    |          |              |         |           |                                                                                 |                                                                         |
|                  | VECTOR                      | Tezepelumab versus placebo | Moderate-to-severe asthma, 12–21 years | 100 | Recruiting estimated | Q4W          | IIIb    | 16-week treatment + 12-week follow-up (influenza vaccine at week 12) | Potential effect of tezepelumab on antibody responses following seasonal quadrivalent influenza virus vaccination in the fall/winter 2021–2022 in the United States. |                                                                         |

AI, autoinjector; APFS, single-use accessorized pre-filled syringe; HCP, healthcare professionals; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LOAC, loss of asthma control; OCS, oral corticosteroids; PC20, provocation concentration of methacholine causing a 20% fall in FEV1; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, once weekly; RCT, randomized controlled trial; V-S, vial-and-syringe.
Expert opinion
In this section, we consider the general challenges faced with the use of current licensed and unlicensed biologics in patients with uncontrolled asthma; this theme extends to the two biologics considered in this review. We also discuss aspects relevant specifically to dupilumab and tezepelumab.

General challenges with biologics in severe asthma
Our enhancing knowledge of asthma phenotypes and endotypes has facilitated careful identification of patients apt for biologic therapy and individual treatment plans based on biomarkers, clinical patient characteristics, and comorbidities. The introduction of home/self-administration is a key innovation especially in the current times in patients with asthma, though this has proved effective in other conditions. The Covid-19 pandemic had marked impact on health services globally, needing rapid reorganization using telemedicine in treating and managing patients generally. The use of biologic self-administration was also critical avoiding otherwise probable delays and interruptions in initiation and maintenance of biologics in severe asthma patients. Not only would these strategies help in patient management and their complex treatment regimens but also potentially drug adherence, their convenience, reduce costs, complications, and also reducing the carbon footprint. Thus, careful selection of subjects suitable for self-administration is essential, with appropriate home therapy training and support of healthcare professionals in the community and hospital to maintain their engagement and empowerment to enhance therapy adherence. There is data in the literature on safe self-administration of biologics in patients with asthma.32,37,50-54 While there may be perks in self-administration of biologics in severe asthma, they may be associated with challenges including needle phobia, fear and anxiety, injection-site reactions and pain, non-adherence, erroneous administration, and lack of patient faith.55,56

The use of OCS in the management of flare-ups of asthma, especially severe asthma, both in the short- and long-term is associated with adverse effects.57 This may increase with aggregate doses and add to the challenges in managing patients with severe asthma. Importantly, with the Covid-19 pandemic on us, there is an association of increased Covid-19-related mortality in uncontrolled asthma patients needing OCS, though per se no increased severe Covid-19-related morbidity associated with asthma as a condition.58,59 Hence, OCS-sparing therapies in the management of severe asthma are pivotal. Some licensed biologics (mepolizumab, benralizumab, and dupilumab) have reported these benefits besides clinical ones to attenuate the disease burden;34,60,61 however, this has not been demonstrated with others (reslizumab and unlicensed tezepelumab).48

As a result of the increase in available monoclonal antibodies in severe asthma, non-responder subjects may benefit from switching biologic treatments. A minimum of 4-month trial is needed to define treatment response, and reduction of OCS in steroid-dependent patients is one of the more reliable marker of therapeutic success.63 However, due to the recent approval of dupilumab in severe asthma, there is limited literature with regard to switching of any licensed biologic to dupilumab, and similarly for tezepelumab.64

Healthcare providers may be in a challenging position choosing the appropriate biological therapy for patients with severe asthma as there is a lack of clinical trial data comparing (licensed and unlicensed) biological therapies in terms of efficacy, real-life effectiveness and safety, especially with prolonged use. When considering a patient for a biologic agent, a number of patient-specific criteria may be worth considering including age of asthma onset, coexisting conditions (atopic dermatitis and rhinitis, nasal polyposis), the number of asthma exacerbations, OCS use, lung function, subjective asthma assessments, and biomarkers (FeNO, sputum and blood eosinophil, total and aero-allergen-specific IgE levels).65 Comorbidities have an impact on the choice of the biological treatment in severe asthma. Asthma associated with atopic dermatitis favors dupilumab, whereas patients with asthma and chronic rhinosinusitis with nasal polyps significantly improved both with dupilumab, anti-IgE, or anti IL-5 treatment.66

In addition, logistical consideration may be needed in terms of cost, insurance cover, delivery method, and frequency. Once instituted on treatment, it may be prudent to monitor things in terms of efficacy and safety on a pre-determined
regime (personalized) with the patient of 4–6 monthly. Also, in the absence of well-defined criteria to assess clinical response, setting of goals would be important at follow-up visits, such as exacerbation frequency, OCS use, healthcare utilization, subjective asthma parameters, lung function, and impact on co-morbid conditions, to determine whether ongoing biologic therapy is appropriate or not. Of note, response needs to be considered in light concordance with therapy, especially in patients self-administering in the community. Hence, what would be ideal is a biomarker(s) that may not only help to determine prediction of therapeutic response in patients but also those that would aid in the monitoring response. Studies to address these challenges may be helpful in the management of these patients; besides pragmatic head-to-head studies using different biologics to determine optimal efficacy and safety, especially in view of the high costs associated with these agents.

In certain patients, despite being on biologics, there may be persistence of some biomarkers and uncontrolled asthma and in others absence of benefit; in these patients, it may be vital to re-evaluate the asthma phenotype using the currently available biomarkers to determine if they would benefit from and alternative biologic. In the former group where there may be a partial benefit theoretically, one may consider an additional biologic depending on the biomarker profile if appropriate; however, this is not recommended in view of the augmented costs and the lack of evidence of this approach both from an efficacy and safety perspective. Hence, targeted biologics should be offered to those who are likely to benefit from them and monitored for their efficacy. Occasionally, the subtherapeutic responses may be associated with the development of neutralizing anti-drug antibodies. In these situations, therapeutic drug monitoring should be considered. Of note, the risk of immunogenicity is unknown in patients with severe asthma.

Another aspect remains unanswered is the duration for the use of these expensive biologic therapies in patients with severe asthma as they clearly have an impact on public and personal resources if continued indefinitely. With respect to this, there is a crucial need to conduct long-term studies to ascertain the impact of these agents on the course of the condition, such as immunomodulation, resulting in a decline in the severity of the condition or it remission.

Although the efficacy and safety of biologics have been conducted in trials globally, there remain certain patient-groups that have been underrepresented or a paucity of data in some special populations, such as children and adolescents, pregnancy, black ethnic minority. More efforts are needed by researchers to evaluate currently available and future biological therapies in these special groups to enable appropriate and unbiased healthcare in all community groups with asthma.

**Dupilumab**

As aforementioned, there are several clinical studies underway using dupilumab. Not only are these being undertaken to ascertain efficacy and safety, but importantly trying to assess some of the challenges of special populations of adolescents but also in combination with other biologics. More importantly, a head-to-head study comparing the efficacy dupilumab, omalizumab, and placebo in patients with co-morbidity of nasal polyposis has been planned (NCT04998604). Other studies have been planned to assess the effects of dupilumab therapy on physiological parameters of lung function, including post-bronchodilator FEV1, PC20 methacholine challenge, exercise capacity, sleep hygiene, and in sputum and mucociliary clearance. Aspirin-induced respiratory disease may be a challenge to manage; the manufacturers of dupilumab have also planned an open-labeled study to evaluate the effect of dupilumab in this patient group in terms of the maximal aspirin dose tolerated. All these studies may add to the evidence base of dupilumab in patients with asthma and possibly expand its use in some specific patient-groups and those with comorbidities that may be challenging to manage. These trials that are planned/ongoing are summarized in Table 1. Future studies should also be planned comparing dupilumab (head-to-head) with other biologics and ongoing long-term safety surveillance.

With the use of biologics, there is concern on their safety especially with regard to the risk of anaphylaxis. The reported risk of anaphylaxis with the use of omalizumab, reslizumab, mepolizumab, and dupilumab are around 0.2%, 0.33%,
The absence of observed anaphylactic reactions with the latter may be due to high degree of humanization (99%) in its production compared to the others which have approximately 90% humanized components; this results with immunogenicity due to the use of transgenic mouse lines which are unable to generate humanized carbohydrate side chains. Another concern regarding the use of biologic therapies is the development of anti-drug antibodies (ADA), particularly with neutralizing activity. Results of a long-term studies having enrolled moderate-to-severe asthma patients treated with dupilumab for 96 weeks have shown the occurrence of ADA in 7.6% of non-OCS-dependent patients without effects on safety and efficacy of the treatment.

An important aspect observed during administration of dupilumab therapy is the development of eosinophilia in a small proportion of patients as observed in the multiple clinical trials conducted to date. These findings did not impact on the clinical efficacy of dupilumab or manifest any significant symptoms in the patients. Similarly, antibodies to dupilumab have been noted in though have had no observed negative impact of the safety or efficacy in patients. In both, the etiology is unclear, though may be something worth being aware of and to monitor by clinicians who plan to or already have patients on dupilumab therapy.

Dupilumab, first approved in 2017 for atopic dermatitis treatment, received in 2018 by the US Food and Drug Administration (FDA) supplemental biologics license application for patients with severe asthma. In March 2019, the European Medicines Agency’s Committee for Medical Products for Human Use (CHMP) on the basis of clinical data from 2888 adults and adolescents who participated in three pivotal trials from the global LIBERTY ASTHMA program, including the phase III QUEST and VENTURE trials, has adopted a positive opinion for dupilumab, recommending its approval in the European Union for use in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation. The European Commission approved this indication on May 2019. In October 2021, dupilumab obtained extension of approval as add-on maintenance treatment for children aged 6–11 years with moderate-to-severe asthma.

Tezepelumab
Currently, no biologic therapies are available for use in severe T2 low asthma patients whose clinical and pathological characteristics have been suggested. More research is needed to establish pathophysiological mechanisms driving this asthma pheno-/endotype. The efficacy of tezepelumab in severe uncontrolled asthma patients has be reported in terms of improvements in reductions in exacerbation rates, healthcare utilization, spirometric indices, asthma control, and quality-of-life irrespective of patients’ blood eosinophil counts. The improvements in asthma clinical outcomes observed in previous studies with tezepelumab are probably driven, at least in part, by reductions in eosinophilic airway inflammation, as shown here by reduced airway eosinophil counts regardless of baseline blood eosinophil count. No reduction of neutrophils, CD3+, CD4+ lymphocytes, and subtypes of mast cells was noted in the bronchial submucosa of treated patients. However, tezepelumab also reduced airway hyperresponsiveness to both mannitol and methacholine, with a possible inhibiting action on mast cells, indicating that TSLP blockade might have additional benefits in asthma beyond reducing type 2 airway inflammation. It has been proposed that TSLP may be positioned upstream in the airway inflammatory cascade, which makes it suitable for regulating both the Th1 and Th2 pathway.

In addition, tezepelumab is pending licensing though has completed several studies which dupilumab is still in planning/running presently, such as evaluating the impact on airway inflammation, airway hyperresponsiveness, etc. Although there are number of clinical trials underway/planned, one of the most relevant is the one assessing the efficacy and safety in severe asthma patients on OCS (NCT103406078). Future studies should also be planned in patients with other comorbidities, such as nasal polyposis, head-to-head studies with other biologics, in patients with T2-low inflammation, and ongoing long-term safety surveillance. Neutralizing ADA to tezepelumab has been reported in 0.2% of the enrolled subjects in the NAVIGATOR study both in the active and in the placebo group without effects on safety and efficacy.

Overall, tezepelumab shows great promise in severe uncontrolled asthma patients irrespective
of the T2 inflammation and may prove the stop-gap for patients with T2-low inflammation until novel therapies are available specifically addressing the inflammatory pathway.

In 2018, AstraZeneca received Breakthrough Therapy designation by FDA for tezepelumab, and in December 2021, FDA approved tezepelumab use as an add-on maintenance therapy in adults and children aged 12 years and older with severe asthma independent of the patients’ underlying inflammatory phenotype. The Biologics License Application (BLA) was based on results from the PATHFINDER clinical trial program, including results from the pivotal NAVIGATOR phase III trial.

**Conclusion**

In the last years, the emerging knowledge of asthma phenotypes and endotypes allowed to achieve a deeper identification of patients that may be beneficial from biologic therapy and individual treatment plans based on biomarkers, clinical characteristics, and comorbidities. The development of biological drugs targeting specific pathways related to T2 immune response, such as dupilumab, a humanized IgG4 monoclonal antibody acting on IL-4/IL-13 signaling had shown efficacy as add-on therapy in severe uncontrolled asthmatic patients. However, no biologic therapies are available for use in severe T2 low asthma patients. In this regard, tezepelumab, a humanized monoclonal antibody, which prevents the binding of TSLP to its receptor blocking TSLP, IL-25, and IL-33 signaling may be suitable to act in an upstream position in the airway inflammatory cascade for regulating both the Th1 and Th2 immune responses being a great promise in severe uncontrolled asthma patients irrespective to the T2 inflammation, until new therapies will be available for specifically addressing this inflammatory pathway.

Several clinical studies on dupilumab are ongoing to assess its efficacy, safety, and the effects on lung function, exercise capacity, sleep hygiene, and mucociliary clearance. In particular, some trials are trying to assess challenges of special populations, such as adolescents, and to compare its efficacy in patients with comorbidities. All these studies may strengthen the evidence base of dupilumab in patients with asthma and possibly expand its use in some specific patient-groups. Future studies should also be planned comparing dupilumab (head-to-head) with other biologics and ongoing long-term safety surveillance.

The efficacy of tezepelumab in severe uncontrolled asthma patients has been reported in terms of improvements in exacerbation rates, healthcare utilization, spirometric indices, asthma control, and quality-of-life irrespective of patients’ blood eosinophil counts. Tezepelumab also reduced AHR to mannitol, indicating that TSLP blockade might have additional benefits in asthma beyond reducing T2 airway inflammation. Among the planned clinical trials, the most relevant is the one assessing the efficacy and safety in severe asthma patients on OCS. Future studies should also be planned in patients with other comorbidities, such as nasal polyposis, head-to-head studies with other biologics, in patients with T2-low inflammation, and ongoing long-term safety surveillance.

The introduction of biologic home/self-administration is a key innovation, especially in the current times during COVID-19 pandemic, in patients with asthma and may potentially improve drug adherence, reduce costs, and complications.

There are still unanswered questions that needs to be addressed, that is, the absence of well-defined criteria to assess clinical response setting goals, the lack of clinical trial data comparing biological therapies in terms of efficacy, real-life effectiveness, and safety, especially with prolonged use, the need of biomarker(s) able to determine the prediction of therapeutic response but also aiding in the monitoring response, the duration for the use of these expensive biologic therapies.

**Author contributions**

**Beatrice Ragnoli**: Conceptualization; Writing – original draft.

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Ethical approval from an institutional review board and consent to participate were not required for this review.

Consent for publication
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