Dupilumab and tezepelumab in severe refractory asthma: new opportunities

Beatrice Ragnoli*, Jaymin Morjaria*, Patrizia Pignatti, Paolo Montuschi, Mariangela Barbieri, Lucrezia Mondini, Luca Ruggero, Liliana Trotta and Mario Malerba

Ther Adv Chronic Dis

2022, Vol. 13: 1–19

DOI: 10.1177/20406223221097327

***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

Received: 16 February 2022; revised manuscript accepted: 11 April 2022.

Correspondence to:

Mario Malerba
Department of Translational Medicine, University of Eastern Piedmont, 28100 Novara, Italy

Respiratory Unit, S. Andrea Hospital, Vercelli, Italy
mario.malerba@uniupo.it

Beatrice Ragnoli
Mariangela Barbieri
Lucrezia Mondini
Luca Ruggero
Liliana Trotta
Respiratory Unit, S. Andrea Hospital, Vercelli, Italy

Jaymin Morjaria
Department of Respiratory Medicine, Harefield Hospital, Guy's & St Thomas' NHS Foundation Trust, Harefield, UK

Patrizia Pignatti
Allergy and Immunology Unit, Istituti Clinici Scientifici Maugeri IRCCS Pavia, Pavia, Italy

Paolo Montuschi
Pharmacology Department, Faculty of Medicine, Catholic University of the Sacred Heart, Milan, Italy

Airways Disease Section, National Heart and Lung Institute, Faculty of Medicine, Imperial College of Science Technology and Medicine, London, UK

*BR and JM contributed equally to the writing of the manuscript.

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.[5] 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.[6]

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.[7,8]

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.[9] Several biologics have been developed which are able to attenuate or abolish specific inflammatory pathways, with the aim of providing enhanced personalized asthma treatment.[10]

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 biological therapies approved for severe asthmatic patients, and a great amount of studies have been provided showing their efficacy.[11] 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.[12]

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 IL4R 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.[13] Dupilumab is able to bind both IL-4 receptor types inhibiting their signaling.[14]

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.[15]

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.[16,17] IL-4 and IL-13's pathways and dupilumab's action are shown in Figure 1.

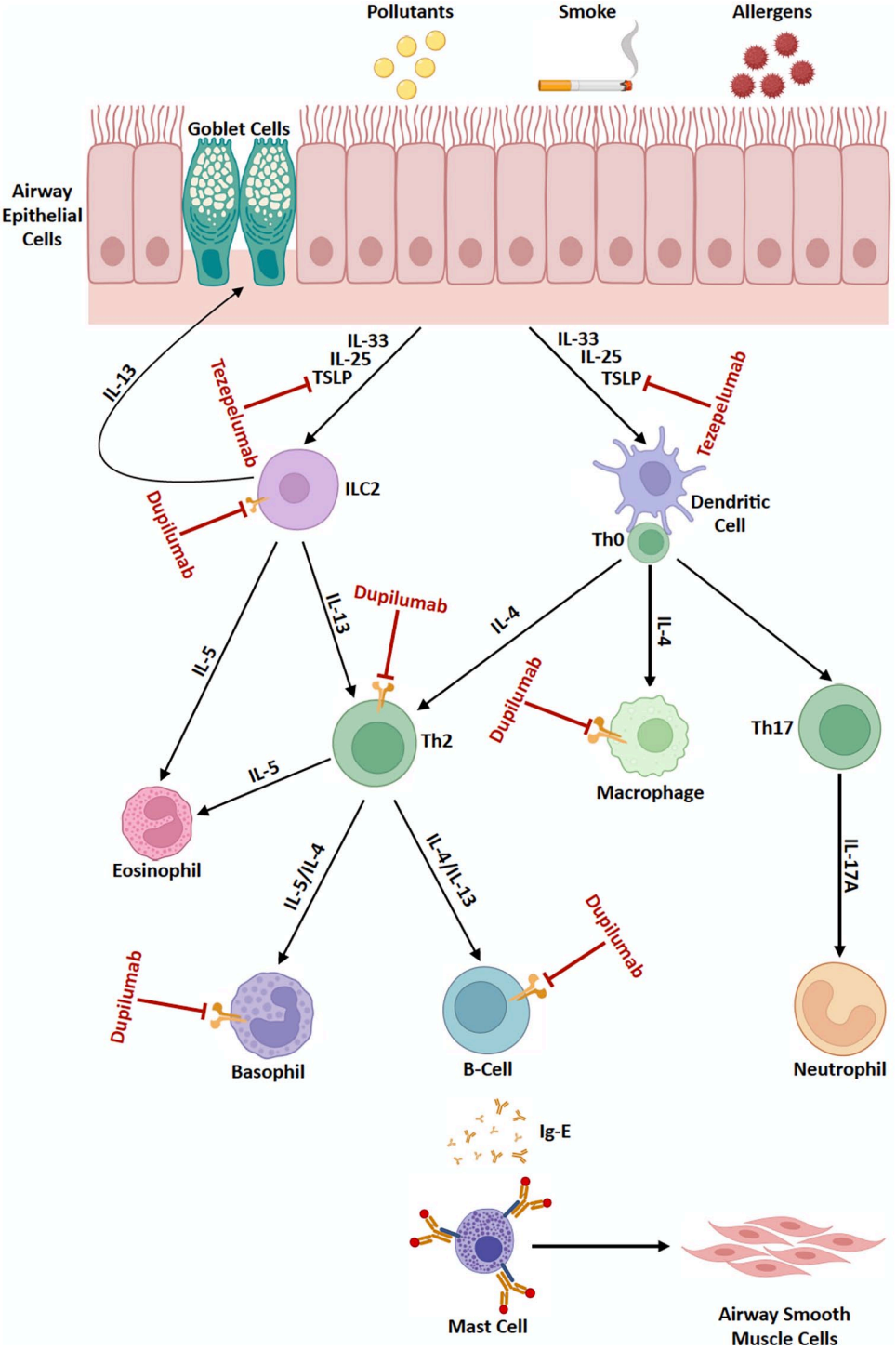

Figure 1. Dupilumab and tezepelumab's mechanisms and pathways. Dupilumab exerts a dual blockade of IL-4 and IL-13 signaling inducing beneficial effects in T2 phenotypes. Tezepelumab prevents binding of TSLP to its receptor blocking TSLP, IL-25, and IL-33 signaling. Acting in an upstream position in the 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.[25] 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,[28] 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 prefilled 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.*[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,[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.[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.[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.[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%).[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.[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.[36] 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.[37] 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.[38] Similar to the study by Wenzel *et al.*,[30] 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.[39] 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.[26] 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 NCT02414854, 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 FEV_1
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 (AAER)	Lower rate of exacerbations in patients treated with dupilumab
LIBERTY ATHMA TRAVERSE NCT02134028, Wechsler *et al.*	Dupilumab	[37]	Patients with asthma who participated in a previous dupilumab asthma study (DRI12544, PDY14192, EFC13579, and EFC13691)	2282	Open label	Q2W	III	108 weeks	Long-term safety and tolerability	The data verified the safety of dupilumab up to 148 weeks of treatment
NCT03387852, Wechsler *et al.*	SAR440340/REGN3500 Monotherapy sc *versus* dupilumab *versus* SAR440340/ 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
NCT04022447, Dupin *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)

Table 1. (Continued)

Studies	Drugs	Ref	Population	*n*	Design	Dose	Phase	Follow-up	Primary outcome	Results
Ongoing studies										
NCT03112577	REGN3500 (itepekimab) ev *versus* dupilumab sc *versus* REGN3500 ev + dupilumab sc *versus* placebo		Adults with mild allergic asthma	32	RCT		I	42 weeks	Difference in BAC-induced changes in sputum inflammatory markers in individuals treated with REGN3500, dupilumab and the combination of REGN3500 plus dupilumab or placebo	
EXPEDITION, NCT02573233	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 LTS12551 (TRAVERSE)	750	Open-label interventional	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	Not yet 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-4RαR576 gene variant	Recruiting estimated 150	RCT	Two doses on day 1 followed by Q2W	IV	48-week treatment	Rate of asthma exacerbations	
NCT04203797	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	Not yet recruiting Estimated 15	Single-group assignment	Two doses on day 1 followed by Q2W	IV	16 weeks	Effects on dupilumab on respiratory microbiota	
NCT04442256	Dupilumab		AERD–Aspirin-exacerbated 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 Smell Identification Test	
MORPHEO 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	Not yet recruiting estimated 30	RCT	Two doses on day 1 followed by Q2W	IV	12 weeks	Change in mucociliary clearance (MCC) rate	

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 submucosal eosinophils ratio of geometric least-squares means [0.15 (95% CI, 0·05–0·41); nominal $p<0.0010$], 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[44] 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 NCT03989544, Zheng *et al.*	Tezepelumab (V-S) *versus* tezepelumab (APFS) *versus* tezepelumab (AI)	[29]	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 NCT02054130, Corren *et al.*	Tezepelumab 70 mg Q4W *versus* tezepelumab 210 mg Q4W *versus* tezepelumab 280 mg Q2W *versus* placebo	[26]	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 NCT03688074, *Diver al.* and Emson *et al.*	Tezepelumab *versus* placebo	[40,46]	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 NCT02698501, Sverrill *et al.*	Tezepelumab *versus* placebo	[41]	Adults with asthma and AHR to mannitol	40	RCT	Q4W	II	12 weeks	Changes in AHR to mannitol Changes in airway inflammation	Reduced AHR Reduced eosinophilic inflammation
PATH-HOME NCT03968978, Alpizar *et al.*	Tezepelumab (APFS) *versus* tezepelumab (AI)	[42]	Adults and adolescents with severe asthma	216	Open-label randomized	Q4W	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 NCT03347279, Menzies-Gow *et al.*	Tezepelumab *versus* placebo	[27,47]	Adults and adolescents with severe asthma	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	[43]	Adults and adolescents with severe asthma	550	RCT	Q4W	IIb	52 weeks	Determine serum IL-5 and IL-13 levels in PATWHAY participants	IL-5 and IL-13 levels were higher in patients with severe asthma. After 52-week tezepelumab-reduced 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	[44]	Adults and adolescents with severe asthma	550	RCT		IIb	52 weeks	AAER	Tezepelumab treatment reduced numbers of AAER across all seasons
Corren *et al.*	Tezepelumab 70 mg Q4W *versus* tezepelumab 210 mg Q4W *versus* tezepelumab 280 mg Q2W *versus* placebo	[45]	Adults and adolescents with severe asthma	550	RCT		IIb	52 weeks	Efficacy of tezepelumab in PATHWAY participants with permanent allergy	Tezepelumab reduced the AAER *versus* placebo by 66–78% in patients with perennial allergy
Emson *et al.*	Tezepelumab 210 mg *versus* placebo	[46]	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										
DIRECTION-CK NCT04362410	Tezepelumab low dose *versus* tezepelumab medium dose *versus* tezepelumab high dose *versus* placebo		Healthy subject	48	RCT	Single dose	I	28 days	Evaluate the pharmacokinetics, safety, tolerability, and immunogenicity	
NCT04673630	Tezepelumab		Children (5–11 years) with asthma	14	Open label	Single dose	I	85 days	Pharmacokinetic of tezepelumab in children	
SOURCE NCT03406078, Wechsler *et al.*	Tezepelumab *versus* placebo	[48]	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	
DIRECTION NCT03927157, Zhong *et al.*	Tezepelumab *versus* placebo		Adults and adolescents with severe asthma	Recruiting estimated 396	RCT	Q4W	III	52-week treatment + 12-week follow-up	AAER	
NOZOMI NCT04048343, Shinkai *et al.*	Tezepelumab		Adults and adolescents with severe asthma	65	Open-label single arm study	Q4W	III	52-week treatment + 12-week follow-up	Number of subjects with adverse events	
DESTINATION NCT03706079, Menzies-Gow *et al.*	Tezepelumab *versus* placebo	[49]	Patients who complete the 52- 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	
VECTOR NCT05062759	Tezepelumab *versus* placebo		Moderate-to-severe asthma, 12–21 years	Recruiting estimated 100	RCT	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).[48,62]

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 tezepeleumab.[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;[67] 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.[68]

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.[38] 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.[69] In these situations, therapeutic drug monitoring should be considered. Of note, the risk of immunogenicity is unknown in patients with severe asthma.[70]

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.[71]

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.[53,54,72,73] 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%,

0, and 0, respectively.[74–77] 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.[37]

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.[30,32] 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.[78,79] 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.[27,40,41,43–45] 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.[40] No reduction of neutrophils, CD3+, CD4+ lymphocytes, and subtypes of mast cells was noted in the bronchial submucosa of treated patients.[40] However, tezepelumab also reduced airway hyperresponsiveness to both mannitol[40] and methacholine,[80] 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.[27]

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.
Jaymin Morjaria: Conceptualization; Writing – original draft.
Patrizia Pignatti: Conceptualization; Writing – original draft.
Paolo Montuschi: Conceptualization; Writing – original draft.
Mariangela Barbieri: Conceptualization; Writing – original draft.

Lucrezia Mondini: Conceptualization; Writing – original draft.
Luca Ruggero: Conceptualization; Writing – original draft.
Liliana Trotta: Conceptualization; Writing – original draft.
Mario Malerba: Conceptualization; Writing – original draft; Writing – review & editing.

Availability of data and materials
Not applicable.

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

Consent for publication
Consent for publication was not required for this review as no patients were involved.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was (partially) funded by the AGING Project – Department of Excellence – DIMET, University Piemonte Orientale.

Conflict of interest statement
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JM has received honoraria for speaking and financial support to attend meetings or advisory boards from Wyeth, Chiesi, Pfizer, MSD, Boehringer Ingelheim, Teva, GSK/Allen & Hanburys, Napp, Almirall, AstraZeneca, Trudell, Cook Medical, Medela AG, and Novartis. He has been an expert witness in a court case relating to the impact of smoking on illness severity, ITU admissions and mortality form COVID-19 in South Africa in 2020. The entire proceeds of the work were donated to various charities. He is also an associate editor of *Therapeutic Advances in Chronic Disease*, therefore, the peer-review process was managed by alternative members of the Board, and he had no involvement in the decision-making process. MM has received honoraria for speaking and financial support for attending meetings and serving on the advisory boards from Chiesi, AstraZeneca, GSK, Laboratori Guidotti, and Boehringer Ingelheim. The authors have no other relevant affiliations of financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article apart from those disclosed. The other authors declare no conflicts of interest.

ORCID iD
Beatrice Ragnoli https://orcid.org/0000-0001-5969-8501

References
1. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma–summary report 2007. *J Allergy Clin Immunol* 2007; 120: S94–138.
2. Sears MR. Trends in the prevalence of asthma. *Chest* 2014; 145: 219–225.
3. Fahy JV. Type 2 inflammation in asthma – present in most, absent in many. *Nat Rev Immunol* 2015; 15: 57–65.
4. Southworth T, Van Geest M and Singh D. Type-2 airway inflammation in mild asthma patients with high blood eosinophils and high fractional exhaled nitric oxide. *Clin Transl Sci* 2021; 14: 1259–1264.
5. Menzies-Gow A, Mansur AH and Brightling CE. Clinical utility of fractional exhaled nitric oxide in severe asthma management. *Eur Respir J* 2020; 55: 1901633.
6. Kuruvilla ME, Lee FE and Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. *Clin Rev Allergy Immunol* 2019; 56: 219–233.
7. Peters SP, Jones CA, Haselkorn T, *et al.* Real-world evaluation of asthma control and treatment (REACT): findings from a national web-based survey. *J Allergy Clin Immunol* 2007; 119: 1454–1461.
8. Canonica GW, Colombo GL, Bruno GM, *et al.* Shadow cost of oral corticosteroids-related adverse events: a pharmacoeconomic evaluation applied to real-life data from the Severe Asthma Network in Italy (SANI) registry. *World Allergy Organ J* 2019; 12: 100007.
9. Malerba M, Radaeli A, Mancuso S, *et al.* The potential therapeutic role of potassium channel modulators in asthma and chronic obstructive pulmonary disease. *J Biol Regul Homeost Agents* 2010; 24: 123–130.

10. Moore WC, Meyers DA, Wenzel SE, *et al.* Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med* 2010; 181: 315–323.
11. Papathanassiou E, Loukides S and Bakakos P. Severe asthma: anti-IgE or anti-IL-5? *Eur Clin Respir J* 2016; 3: 31813.
12. Fitzpatrick AM, Chipps BE, Holguin F, *et al.* T2-"Low" asthma: overview and management strategies. *J Allergy Clin Immunol Pract* 2020; 8: 452–463.
13. Grinich EE and Simpson EL. Additional biologic therapeutics: dupilumab, omalizumab, others. In: Wolverton SE (ed.) *Comprehensive dermatologic drug therapy*. 4th ed. Amsterdam: Elsevier, 2021, pp. 339–348.e4.
14. Ricciardolo FLM, Bertolini F and Carriero V. The role of dupilumab in severe asthma. *Biomedicines* 2021; 9: 1096.
15. Santini G, Mores N, Malerba M, *et al.* Dupilumab for the treatment of asthma. *Expert Opin Investig Drugs* 2017; 26: 357–366.
16. Pelaia C, Crimi C, Vatrella A, *et al.* Molecular targets for biological therapies of severe asthma. *Front Immunol* 2020; 11: 603312.
17. Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 2008; 118: 3546–3556.
18. Laidlaw TM, Bachert C, Amin N, *et al.* Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma. *Ann Allergy Asthma Immunol* 2021; 126: 584–592.
19. Pelaia C, Lombardo N, Busceti MT, *et al.* Short-term evaluation of dupilumab effects in patients with severe asthma and nasal polyposis. *J Asthma Allergy* 2021; 14: 1165–1172.
20. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf
21. Zhang L, Gao Y, Li M, *et al.* Population pharmacokinetic analysis of dupilumab in adult and adolescent patients with asthma. *CPT Pharmacometrics Syst Pharmacol* 2021; 10: 941–952.
22. Nakajima S, Kabata H, Kabashima K, *et al.* Anti-TSLP antibodies: targeting a master regulator of type 2 immune responses. *Allergol Int* 2020; 69: 197–203.
23. Verstraete K, Peelman F, Braun H, *et al.* Structure and antagonism of the receptor complex mediated by human TSLP in allergy and asthma. *Nat Commun* 2017; 8: 14937.
24. Pelaia C, Pelaia G, Crimi C, *et al.* Tezepelumab: a potential new biological therapy for severe refractory asthma. *Int J Mol Sci* 2021; 22: 4369.
25. Ambrose CS, *et al.* Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. *Expert Opin Ther Targets* 2020; 24: 777–792.
26. Corren J, Parnes JR, Wang L, *et al.* Tezepelumab in Adults with Uncontrolled Asthma. *N Engl J Med* 2017; 377: 936–946.
27. Menzies-Gow A, Corren J, Bourdin A, *et al.* Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med* 2021; 384: 1800–1809.
28. Smith SG, Chen R, Kjarsgaard M, *et al.* Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. *J Allergy Clin Immunol* 2016; 137: 75–86.
29. Zheng Y, Abuqayyas L, Megally A, *et al.* Tezepelumab pharmacokinetics, safety, and tolerability after administration via vial-and-syringe, accessorized prefilled syringe, or autoinjector: a randomized trial in healthy volunteers. *Clin Ther* 2021; 43: 142–155.e5.
30. Wenzel S, Ford L, Pearlman D, *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; 368: 2455–2466.
31. Wenzel S, Castro M, Corren J, *et al.* Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet Lond Engl* 2016; 388: 31–44.
32. Castro M, Corren J, Pavord ID, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; 378: 2486–2496.
33. Castro M, Rabe KF, Corren J, *et al.* Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma. *ERJ Open Res* 2020; 6: 0024-2019.
34. Rabe KF, Nair P, Brusselle G, *et al.* Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *N Engl J Med* 2018; 378: 2475–2485.

35. Maspero JF, FitzGerald JM, Pavord ID, *et al*. Dupilumab efficacy in adolescents with uncontrolled, moderate-to-severe asthma: liberty asthma quest. *Allergy* 2021; 76: 2621–2624.

36. Bacharier LB, Maspero JF, Katelaris CH, *et al*. Dupilumab in children with uncontrolled moderate-to-severe asthma. *N Engl J Med* 2021; 385: 2230–2240.

37. Wechsler ME, Ford LB, Maspero JF, *et al*. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. *Lancet Respir Med* 2022; 10: 11–25.

38. Wechsler ME, Ruddy MK, Pavord ID, *et al*. Efficacy and safety of itepekimab in patients with moderate-to-severe asthma. *N Engl J Med* 2021; 385: 1656–1668.

39. Dupin C, Belhadi D, Guilleminault L, *et al*. Effectiveness and safety of dupilumab for the treatment of severe asthma in a real-life French multi-centre adult cohort. *Clin Exp Allergy* 2020; 5050: 789–798, https://pubmed.ncbi.nlm.nih.gov/32469092/ (accessed 4 February 2022).

40. Diver S, Khalfaoui L, Emson C, *et al*. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2021; 9: 1299–1312.

41. Sverrild A, Hansen S, Hvidtfeldt M, *et al*. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). *Eur Respir J* 2021; 59: 2101296.

42. Alpizar S, Megally A, Chen C, *et al*. Functionality and performance of an accessorized pre-filled syringe and an autoinjector for at-home administration of tezepelumab in patients with severe, uncontrolled asthma. *J Asthma Allergy* 2021; 14: 381–392.

43. Pham TH, Chen C, Colice G, *et al*. Tezepelumab normalizes serum interleukin-5 and -13 levels in patients with severe, uncontrolled asthma. *Ann Allergy Asthma Immunol* 2021; 127: 689–691.

44. Corren J, Karpefors M, Hellqvist Å, *et al*. Tezepelumab reduces exacerbations across all seasons in patients with severe, uncontrolled asthma: a post hoc analysis of the pathway phase 2b study. *J Asthma Allergy* 2021; 14: 1–11.

45. Corren J, Ambrose CS, Sałapa K, *et al*. Efficacy of tezepelumab in patients with severe, uncontrolled asthma and perennial allergy. *J Allergy Clin Immunol Pract* 2021; 9: 4334–4342.

46. Emson C, Corren J, Sałapa K, *et al*. Efficacy of tezepelumab in patients with severe, uncontrolled asthma with and without nasal polyposis: a post hoc analysis of the phase 2b pathway study. *J Asthma Allergy* 2021; 14: 91–99.

47. Menzies-Gow A, Colice G, Griffiths JM, *et al*. NAVIGATOR: a phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. 2020; 21: 266, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550847/ (accessed 10 November 2021).

48. Wechsler ME, Colice G, Griffiths JM, *et al*. SOURCE: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. *Respir Res* 2020; 21: 264.

49. Menzies-Gow A, Ponnarambil S, Downie J, *et al*. DESTINATION: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma. *Respir Res* 2020; 21: 279, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7576983/ (accessed 10 November 2021).

50. Menzella F, Galeone C, Formisano D, *et al*. Real-life efficacy of omalizumab after 9 years of follow-up. *Allergy Asthma Immunol Res* 2017; 9: 368–372.

51. Khurana S, Brusselle GG, Bel EH, *et al*. Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: the COSMEX study. *Clin Ther* 2019; 41: 2041–2056.

52. Korn S, Bourdin A, Chupp G, *et al*. Integrated safety and efficacy among patients receiving benralizumab for up to 5 years. *J Allergy Clin Immunol Pract* 2021; 9: 4381–4392.

53. Oh SS, White MJ, Gignoux CR, *et al*. Making precision medicine socially precise. Take a deep breath. *Am J Respir Crit Care Med* 2016; 193: 348–350.

54. Samedy-Bates LA, Oh SS, Nuckton TJ, *et al*. Racial/Ethnic-Specific Differences in the Effects of Inhaled Corticosteroid Use on Bronchodilator Response in Patients With Asthma. *Clin Pharmacol Ther* 2019; 106: 1133–1140.

55. Kishimoto M, Yamairi F, Sato N, *et al*. Patient preference for treatment mode of biologics in

rheumatoid arthritis: a 2020 web-based survey in Japan. *Rheumatol Ther* 2021; 8: 1095–1111.

56. Sanz-Gil R, Pellicer A, Montesinos MC, *et al.* Improved effectiveness from individualized dosing of self-administered biologics for the treatment of moderate-to-severe psoriasis: a 5-year retrospective chart review from a Spanish University Hospital. *J Dermatolog Treat* 2020; 31: 370–377.
57. Bleecker ER, Menzies-Gow AN, Price DB, *et al.* Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med* 2020; 201: 276–293.
58. Liu S, Cao Y, Du T, *et al.* Prevalence of comorbid asthma and related outcomes in COVID-19: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 2021; 9: 693–701.
59. Williamson EJ, Walker AJ, Bhaskaran K, *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; 584: 430–436.
60. Taillé C, Chanez P, Devouassoux G, *et al.* Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme. *Eur Respir J* 2020; 55: 1902345.
61. Nair P, Wenzel S, Rabe KF, *et al.* Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; 376: 2448–2458.
62. Bernstein JA, Virchow JC, Murphy K, *et al.* Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2020; 8: 461–474.
63. GINA Main Report. 2021 global initiative for asthma – GINA, https://ginasthma.org/gina-reports/ (accessed 28 March 2022).
64. Papaioannou AI, Fouka E, Papakosta D, *et al.* Switching between biologics in severe asthma patients. When the first choice is not proven to be the best. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 2021; 51: 221–227.
65. Krings JG, McGregor MC, Bacharier LB, *et al.* Biologics for severe asthma: treatment-specific effects are important in choosing a specific agent. *J Allergy Clin Immunol Pract* 2019; 7: 1379–1392.
66. Kavanagh JE, Hearn AP and Jackson DJ. A pragmatic guide to choosing biologic therapies in severe asthma. *Breathe (Sheff)* 2021; 17: 210144.
67. Israel E, Denlinger LC, Bacharier LB, *et al.* PrecISE: precision medicine in severe asthma: an adaptive platform trial with biomarker ascertainment. *J Allergy Clin Immunol* 2021; 147: 1594–1601.
68. Pilette C, Brightling C, Lacombe D, *et al.* Urgent need for pragmatic trial platforms in severe asthma. *Lancet Respir Med* 2018; 6: 581–583.
69. Corren J, Du E, Gubbi A, *et al.* Variability in blood eosinophil counts in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract* 2021; 9: 1224–1231.
70. Kavanagh JE, Hearn AP, Dhariwal J, *et al.* Real-world effectiveness of benralizumab in severe eosinophilic asthma. *Chest* 2021; 159: 496–506.
71. Menzies-Gow A, Bafadhel M, Busse WW, *et al.* An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol* 2020; 145: 757–765.
72. Middleton PG, Gade EJ, Aguilera C, *et al.* ERS/TSANZ Task Force Statement on the management of reproduction and pregnancy in women with airways diseases. *Eur Respir J* 2020; 55: 1901208.
73. Pfaller B, José Yepes-Nuñez J, Agache I, *et al.* Biologicals in atopic disease in pregnancy: an EAACI position paper. *Allergy* 2021; 76: 71–89.
74. Harrison RG, MacRae M, Karsh J, *et al.* Anaphylaxis and serum sickness in patients receiving omalizumab: reviewing the data in light of clinical experience. *Ann Allergy Asthma Immunol* 2015; 115: 77–78.
75. Ma L, Danoff TM and Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. *J Allergy Clin Immunol* 2014; 133: 1075–1083.
76. Leung E, Al Efraij K and FitzGerald JM. The safety of mepolizumab for the treatment of asthma. *Expert Opin Drug Saf* 2017; 16: 397–404.
77. Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, *et al.* Hypersensitivity reactions to therapeutic monoclonal antibodies: phenotypes and endotypes. *J Allergy Clin Immunol* 2018; 142: 159–170.
78. Christiansen SC and Zuraw BL. Treatment of hypertension in patients with asthma. *N Engl J Med* 2019; 381: 1046–1057.
79. Hinks TSC, Levine SJ and Brusselle GG. Treatment options in type-2 low asthma. *Eur Respir J* 2021; 57: 2000528.
80. Gauvreau GM, O'Byrne PM, Boulet LP, *et al.* Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med* 2014; 370: 2102–2110.