New perspectives of biological therapy for severe asthma in adults and adolescents

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Summary

Severe asthma is associated with increased morbidity, mortality, healthcare costs and impaired quality of life. Asthma is no longer considered as a single entity but as a heterogeneous disease with different clinical presentations (phenotypes) and variable underlying mechanistic biological pathways (endotypes). Two different endotypes are based on the inflammatory Type 2 T-helper response: T2-high and T2-low. The understanding of these endotypes has revolutionised the management of severe asthma. Recent guidelines from the 2019 European Respiratory Society/American Thoracic Society (ERS/ATS) and Global Initiative for Asthma (GINA) 2021 specifically address the diagnosis and the management of severe asthma in adults, but less evidence exists for the paediatric population. Presently, five biologics for the treatment of severe asthma are approved, i.e., omalizumab (anti-IgE antibody), mepolizumab and reslizumab (anti-IL-5 antibody), benralizumab (anti-IL-5 receptor antibody) and dupilumab (anti-IL-4 receptor alpha antibody). This article reviews the pathological mechanisms of severe asthma, clinical biomarkers related to the T2-high endotype, and their use for the prediction of the severity of the disease and response to biological therapy. Furthermore, future developments of biologics for severe asthma are presented.

Introduction

Asthma is one of the most common chronic respiratory diseases [1], affecting an estimated 250 million persons worldwide [2]. Despite optimal treatment, severe asthma remains uncontrolled in a minority of asthmatic patients, about 4–10% of adults [3] and 5% of children [4]. The underlying immunopathological mechanisms of asthma cause a heterogeneous chronic airway inflammation, leading to long-term airway remodelling, a process of irreversible structural changes in the bronchial architecture [5]. Modern management of asthma is increasingly taking into account its heterogeneity and complexity, including different phenotypes and endotypes [6]. Biological therapies represent a new era that revolutionises the treatment of severe asthma. Since the introduction of the first monoclonal antibody, omalizumab, an anti-IgE antibody first approved by U.S. Food and Drugs Administration in 2003, an increasing number of new generation of monoclonal antibodies is now available.

Asthma definitions, phenotypes and endotypes

Asthma is characterised by heterogeneous chronic airway inflammation and the presence of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough, all of which fluctuate both in time and intensity, combined with a variable limitation of the expiratory air flow [7].

According to the Global Initiative for Asthma (GINA), difficult-to-treat asthma is defined as asthma that is uncontrolled despite prescription of medium or high-dose inhaled corticosteroids (ICS) combined with long-acting beta-agonists (LABA), or that requires maintaining oral corticosteroids for symptom control and to reduce the risk of exacerbations.

An estimated 17% of asthmatics suffer from difficult-to-treat asthma, in which poor control is due to factors other than asthma itself, including suboptimal adherence to treatment, incorrect inhaler technique, smoking or comorbidities (gastro-oesophageal reflux, chronic rhino-sinusitis, obesity, obstructive sleep apnoea) [7].

Severe asthma is a subset of difficult-to-treat asthma which fails to improve despite confirmation of the diagnosis and adequate treatment of comorbidities and confounding factors, such as inhaler technique, adherence, risk factors, and triggers [7].

Phenotypes and endotypes of asthma

The classical view of asthma as a single disease entity was recently challenged by an expanded understanding of its underlying pathophysiological mechanisms [8]. The recognition of an intricate biological network of distinct and interrelating inflammatory pathways has led to the identification of different asthma phenotypes and endotypes, in particular the Type 2 T-helper response [6]. Clinical phenotypes are defined as observable characteristics resulting from the combination of genetic and environ-

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mental influences [6]. For asthma, the so called "T2-high phenotypes" are classified into three different groups: early-onset eosinophilic allergic asthma, late-onset eosinophilic allergic or non-allergic asthma and aspirin-exacerbated respiratory disease (AERD). On the other hand, "T2-low phenotypes" are associated with clinical characteristics such as obesity, smoking and advanced age [6].

Two major asthma endotypes describe these distinct phenotypes at the cellular and molecular level [6] (figure 1).

T2-High asthma endotype (allergic or non-allergic eosinophilic asthma)

T2-high asthma is orchestrated by T-helper cells type 2 (Th2) and group 2 innate lymphoid cells (ILC2). When stimulated by alarmins, epithelial cytokines released from bronchial epithelial cells in response to stressors such as infection or inflammation, these cells generate abundant amounts of cytokines that lead to IgE antibody production with blood and sputum eosinophilia [6].

IL-4 is the predominant cytokine that drives Th2 differentiation and production of downstream cytokines, including IL-5 and IL-13, as well as B cell activation inducing the class switching and secretion of IgE isotype antibodies [6]. IL-4 and IL-13 bind to a common IL-4Rα chain, promoting goblet cell overexpression, increased mucus secretion, and airway hyper-responsiveness.

In addition to mediating the immediate hypersensitivity response in allergic asthma via activation and degranulation of mast cells, specific IgE antibodies generate a delayed phase reaction in response to allergen exposure, charac-

terised by influx of eosinophils and other inflammatory cells.

IL-5 plays a central role in promoting the differentiation and maturation of eosinophilic progenitors in the bone marrow, as well as their subsequent migration and survival.

Eosinophils can also activate bronchial fibroblasts through the production of profibrotic factors and are thus associated with remodelling characteristics, including the thickening of the basement membrane [6].

T2-Low or non-T2 asthma endotype (neutrophilic asthma)

T2-low or non-T2 asthma endotype is less frequent than T2-high asthma endotype [9] and includes various asthma phenotypes, related to obesity, smoking, occupational exposures, or advanced age/late onset, defined as >50 years or >65 years, depending on the literature source [10, 11]. Such non-eosinophilic asthma refers to the inflammatory endotype of asthma in which non-T2 cytokines play a role in the physiopathology of the disorder. Importantly, this endotype tends to be more resistant to inhaled corticosteroids and presents with a degree of either neutrophilic or pauci-granulocytic inflammation, orchestrated by a range of immune mechanisms such as Th1 and Th17 cytokines (IL-8, IL-17, IL-22), and the alarmins (thymic stromal lymphopoietin (TSLP), IL-25 and IL-33) [6].

For patients with severe asthma, the understanding of their inflammatory endotypes may help to predict severity of asthma and to select the optimal biological therapy [7, 12].

Figure 1: Pathophysiological mechanisms of T2-high asthma. T-helper cells type 2 (Th2) and group 2 innate lymphoid cells (ILC2) when stimulated by alarmins (IL-25, IL-33, TSLP) released by bronchial epithelial cells in response to stressors, produce T2 inflammatory cytokines such as IL-4, IL-5 and IL-13, leading to IgE switching in B cells, degranulation of mast cells, airway eosinophilia, mucus hypersecretion from goblet cells, and smooth muscle contraction resulting in airway hyper-responsiveness. Alarmins can also directly induce mast cells to produce T2 cytokines, and mast cells themselves can produce significant amounts of TSLP following IgE cross-linking. Pathophysiological mechanisms of T2-high asthma. T-helper cells type 2 (Th2) and group 2 innate lymphoid cells (ILC2) when stimulated by alarmins (IL-25, IL-33, TSLP) released by bronchial epithelial cells in response to stressors, produce T2 inflammatory cytokines such as IL-4, IL-5 and IL-13, leading to IgE switching in B cells, degranulation of mast cells, airway eosinophilia, mucus hypersecretion from goblet cells, and smooth muscle contraction resulting in airway hyper-responsiveness. Alarmins can also directly induce mast cells to produce T2 cytokines, and mast cells themselves can produce significant amounts of TSLP following IgE cross-linking.
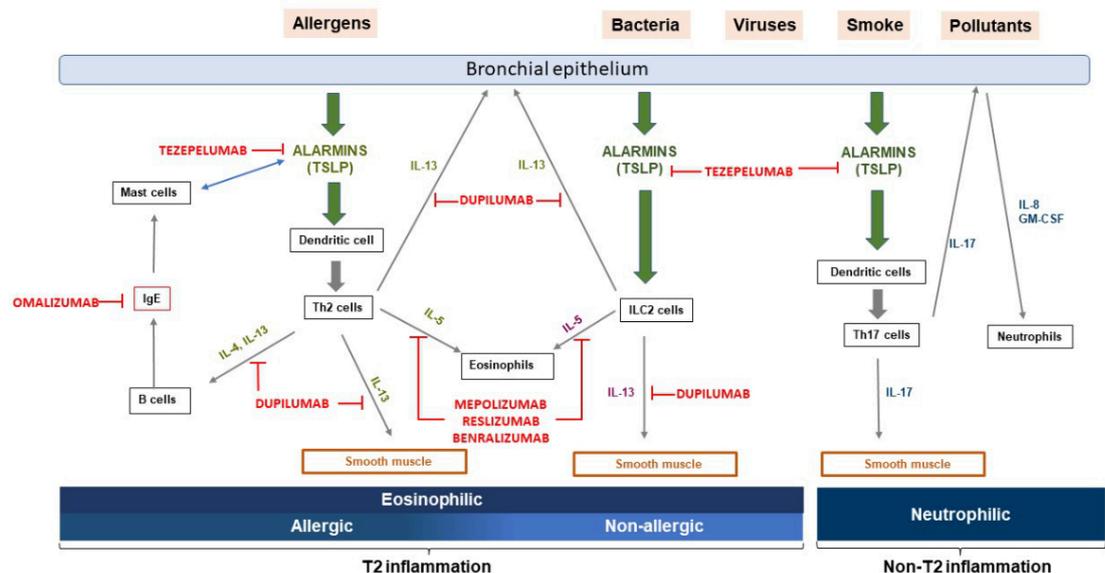
Use of T2 biomarkers to predict severity of asthma and/or response to therapy

An optimal biomarker should be sensitive, specific, straightforward to assess, and provide relevant information. Several biomarkers have been introduced to identify patients with T2 asthma endotypes, predict the severity of the disease, and evaluate response to specific therapies targeting this pathway [13, 14].

Sputum eosinophils: Differential cell counts in sputum is useful to determine profiles of inflammatory cells, i.e. eosinophilic, neutrophilic, pauci-granulocytic or mixed granulocytic [15]. Sputum eosinophils are considered the "gold standard" T2 biomarker (with threshold value >2%) [6, 7]. Nonetheless, considering the risk to perform induced sputum in uncontrolled asthma and requirement of a skilled cytologist able to prepare samples, this method is only performed in specialised centres [6].

Blood eosinophils represent the most commonly used predictive biomarker for T2-high asthma [16]. High levels (>150/µL) predict the risk of more recurrent severe exacerbations, poor asthma control and response to biologics [17].

Exhaled nitric oxide: Nitric oxide is produced by the nitric oxide synthase 2 (iNOS) in the respiratory epithelial cells where it plays a role as an intracellular messenger, inflammatory mediator and vasodilator [18]. FeNO levels >20 parts per billion (ppb) are predictive of the presence of eosinophilic asthma and its response to biologics [9]. Furthermore, elevated FeNO correlate with airway hyper-responsiveness as well as the risk of exacerbations [19, 20].

Serum IgE are used as a marker of atopy and their serum concentrations correlate with the severity of asthma in both adults and children [21].

Serum Periostin: Periostin is an extracellular matrix protein belonging to the fasciclin family that can be upregulated by the type-2 cytokines IL-4 and IL-13 in human bronchial epithelial cells [22]. Serum periostin is associated with eosinophilic airway inflammation and airway remodelling [23]. Levels ≥95 ng/ml are associated with a decline in forced expiratory volume in one second (FEV1) ≥30 ml per year [24]. Furthermore, serum periostin levels correlate with blood eosinophil counts, FeNO and serum total IgE [25]. Of note, serum periostin is not employed as a biomarker in routine clinical practice.

In addition to clinically validated biomarkers of T2 inflammation in asthmatic patients, recent evidence suggests that RNA transcriptomics, and genetic profiling may improve the assessment of asthma, enabling the prediction of severity and response to treatment [26]. *MicroRNAs* are small noncoding RNAs that can be measured in peripheral blood and can regulate gene expression at the post-transcriptional level. The expression of selected microRNA appears to be higher in children with severe asthma [27]. MicroRNA are currently being evaluated as possible biomarkers of outcome as well as exacerbation predictors in severe asthma [28].

Similarly, gene expression [29], exhaled breath analysis [30], and lung microbiome [31] are currently being explored as alternative sources of novel biomarkers.

New options based on T2-high endotypes to treat severe asthma

Based on improved understanding of mechanisms underlying T2 asthma phenotypes and endotypes, the treatment of severe asthma has evolved over the past decade with the development of targeted biologic therapies aiming to downregulate the T2 inflammatory cascade. The 2019 European Respiratory Society/American Thoracic Society (ERS/ATS) and GINA 2021 guidelines recommend using of these new biological agents as add-on therapy for severe uncontrolled asthma [7,12]. However, physicians still face challenges to identify patients who are most likely to respond to a specific targeted therapy and to select the best biological molecules in the absence of direct comparisons between them [32]. Furthermore, the choice of biotherapy is not only based on biomarkers and endotypes but also on clinical features of the patients such as the presence of chronic rhinosinusitis with nasal polyposis or eosinophilic granulomatosis with polyangiitis [33].

To date, five monoclonal antibodies are available for treatment of severe T2 asthma [32, 34].

Table 1:
Clinical features and type 2 inflammatory biomarkers (adapted from Medrek et al. [12]).

Biomarker	Advantages	Disadvantages
Lung function	Routinely use	
	Provide a window into disease control	
	Inverse correlation with blood eosinophils	
Sputum eosinophils	Use for guiding inhaled corticosteroid therapy	Difficult to obtain adequate samples
		Analysis can be challenging and not universally available
Blood eosinophils	Easy to measure	Varying cut-offs are used
	Correlate with sputum eosinophilia and poor asthma control	Can be elevated due to others causes, such as parasitic infection
	Predict the recurrence of severe exacerbations	
FeNO	Predictive for presence of asthma	Requires specialised equipment
	Directly correlated to airway hyper-responsiveness and risk for exacerbations	Several confounding factors including smoking, atopic, use of anti-inflammatory medications
Serum IgE	Easy to measure	Various cut-offs are used
	High levels correlate with severity of asthma	Not useful for assessment of response to anti-IgE
Serum periostin	Higher level associated with decline in FEV1	Can be elevated due to other diseases such as atopic dermatitis, allergic rhinitis, scleroderma, cancer and cardiovascular disease
	Levels correlate with blood eosinophil counts,	Not utilised in clinical routine
	FeNO and serum IgE	

Omalizumab

Omalizumab, a humanised recombinant monoclonal anti-IgE antibody, inhibits binding of free serum IgE to the high affinity surface receptor (FcεRI) on mast cells and basophils [35], which reduces the inflammatory response caused by the activation of such effector cells when interacting with the allergen. Omalizumab has also been shown to have a preventative effect on viral-induced exacerbations in children with allergic asthma by reducing susceptibility to rhinovirus infections [36]. Dendritic cells express the FcεRI receptor on their surface and their antiviral activity is inhibited when IgE binds to surface FcεRI [37]. Omalizumab-dependent reduction of FcεRI expression on dendritic cells enhances antiviral immune responses, reducing the frequency of asthma exacerbations [37].

Serum IgE titer is used to calculate the dose of omalizumab [38], but does not allow prediction of efficacy nor monitoring of treatment response [39]. Peripheral blood eosinophil levels ≥300 cells/µL are associated with an improved response to omalizumab by reducing exacerbations [40].

Several trials have demonstrated that omalizumab significantly decreases the number of severe exacerbations, the dosage of inhaled and oral corticosteroid, and improves patients' quality of life [41,42]. The current 2019 ERS/ATS and GINA guidelines 2021 recommend this monoclonal antibody as an add-on therapy in adolescents and adults with severe allergic asthma with high blood eosinophil counts ≥260 cells/µL or elevated FeNO ≥20 ppb [7,12].

Mepolizumab

Mepolizumab, a human monoclonal antibody directed against IL-5 (anti-IL5), reduces eosinophils and eosinophils precursors in the bone marrow and bronchial mucosa [43]. Several randomised controlled trials in adults and adolescents with severe asthma have shown the efficacy of mepolizumab in reducing blood eosinophilia. This, in turn, lowers the rate of severe exacerbations and the usage of oral corticosteroid while improving asthma controls and increasing lung function [41, 44]. Inclusion in such trials was allowed for patients who met one of the following criteria: patients with blood eosinophil levels ≥150 cells/µL at the time of inclusion, patients on oral corticosteroid, those with blood eosinophils ≥300 cells/µL in the preceding year, or who had had severe recurrent exacerbations in the previous year despite regular use of high-dose inhaled corticosteroid associated with another controller (ICS-LABA). High blood eosinophil count is used as a predictive biomarker of response to mepolizumab [44, 45].

Reslizumab

Reslizumab is a humanised monoclonal antibody anti-IL5, resulting in a reduction of sputum eosinophils and blood eosinophils and, in turn, reduction of exacerbations and asthma symptoms and improved lung function [41,46]. Reslizumab is recommended by the 2019 ERS/ATS and GINA 2021 as an add-on therapy in adults with severe eosinophilic asthma, ≥400 blood eosinophils/µL and a history of asthma exacerbations in previous year [7,12].

Table 2:
Main characteristics and effects of existing biologic therapies against severe asthma based on Global Initiative for Asthma 2021 [7] and Swissmedic recommendations.

Drug name	Omalizumab, XOLAIR ®	Mepolizumab, NUCALA ®	Reslizumab, CINQAERO ®	Benralizumab, FASENRA ®	Dupilumab, DUPIXENT ®	Tezepelumab, TEZSPIRE ®
Target	IgE	IL-5	IL-5	IL-5 receptor a	IL-4 receptor alpha	TSLP
Mode of administration	Subcutaneous injection	Subcutaneous injection	Intravenous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Eligibility criteria	Sensitization to inhaled allergens on skin prick test or specific IgE	Blood eosinophil >300 cells/µL or >150 cells/µL at treatment initiation	Blood eosinophil >400 cells/µL	Blood eosinophil >300 cells/µL	Blood eosinophil >150 cells/µL	Independent from blood eosinophil
	Exacerbations within last year	Exacerbations within last year	Exacerbations within last year	Exacerbations within last year	Exacerbations within last year	T2-low phenotypes?
					FeNO >25 ppb	
					Maintenance OCS	
Other indications	Nasal polyposis	Nasal polyposis			Nasal polyposis	
	Chronic idiopathic urticaria	Eosinophilic granulomatosis with polyangiitis			Moderate-severe atopic dermatitis	
		Hypereosinophilic syndrome				
Age indication	≥6 years	≥6 years	≥18 years	≥18 years	≥12 years	≥12 years
Dosage	75–600 mg (based on weight and tot IgE) every 2 or 4 weeks	100 mg every 4 weeks	3 mg/kg every 4 weeks	30 mg every 4 weeks for 3 doses then every 8 weeks	2 × 300 mg loading dose then 1 × 300 mg every 2 weeks	210 mg every 4 weeks
Expected outcomes	Decreased number of exacerbations	Decreased number of exacerbations	Decreased number of exacerbations	Decreased number of exacerbations	Decreased number of exacerbations	Decreased number of exacerbations
	Improved quality of life	Improved quality of life	Improved lung function and quality of life	Improved lung function and quality of live	Improved lung function ad quality of live	Improved lung function and quality of life
	Minimal effect on FEV1	Decrease oral corticosteroid		Decrease oral corticosteroid	Decrease oral corticosteroid	
		Minimal to moderate effect on FEV1				
Duration of treatment	The GINA 2021 severe asthma guidelines suggest an initial trial of biologic therapy for at least 4 months					
Follow up	Response to add-on biologic therapy should be assessed after 3-4 months and then every 3-6 months, based on: asthma symptom control, frequency and severity of exacerbations, lung function, type 2 comorbidities, side effects, dose of OCS and patient satisfaction					

Benralizumab

Benralizumab, a monoclonal antibody of murine origin that binds the alpha chain of the IL-5 receptor (anti-IL5R) leading to antibody-dependent cell-mediated cytotoxicity and almost complete depletion of eosinophils in the bone marrow, blood and peripheral tissues [47]. Benralizumab reduces administration of oral corticoids, decreases the number of exacerbation and improves both asthma-related quality of life and lung function [41, 48, 49]. Benralizumab is recommended as an add-on therapy in adults and adolescents with severe uncontrolled eosinophilic asthma who have ≥300 blood eosinophils/µL and for those with severe corticosteroid-dependent asthma with at least 2 severe exacerbations in previous year [7, 12].

Dupilumab

The most recently approved biologic, dupilumab, is a fully human monoclonal antibody that binds to the alpha subunit of the IL-4 receptor (mutual to IL-4 and IL-13 receptors), thereby inhibiting both the IL-4 and IL-13 pathway [50]. In patients with severe asthma, dupilumab reduces severe exacerbations and use of oral corticosteroids. In addition, it significantly improves quality of life, symptom controls and lung function [41, 51, 52]. The GINA 2021 guidelines recommend dupilumab as an add-on option for patients with T2-high severe uncontrolled asthma with blood eosinophil level ≥150 cells/µL or FeNO ≥25 ppb or requiring maintenance oral corticosteroids [7]. In contrast, the 2019 ERS/ATS proposes dupilumab as add-on therapy for adult patients with severe eosinophilic asthma and for those severe corticosteroid-dependent asthma regardless of blood eosinophilic counts [12].

The two concerns regarding long term use of biologic therapies are cost and safety. Despite being relatively expensive, the use of these biologics appear to be cost-effective [48]. Efficacy and safety of long term use of biologic treatments are extended up to 148 weeks in dupilumab [53], 156 weeks in mepolizumab [54] and up to 5 years in benralizumab [55].

Future developments of biologics for severe asthma management

Currently, research for next-generation biologics is underway. TSLP, IL-33 and IL-25 are alarmins expressed by airway epithelial cells that have been associated with pathogenesis of asthma and disease severity. These may, therefore, present novel targets for biological therapies in severe asthma [56].

Thymic stromal lymphopoietin (TSLP)

TSLP is produced upstream in the inflammatory cascade by activated lung epithelial cells in response to various environmental insults including viruses, bacteria, fungal products, allergens, chemical irritants and physical injury [57]. In contrast to IL-4, IL-5 or IL-13, TSLP may affect disease activity more widely than a single cytokine acting downstream in the inflammatory cascade [58]. It has been demonstrated that TSLP acts predominantly on dendritic cells, leading to an increase in the T2 inflammatory response (IL-5, IL-4 and IL-13) [59].

Tezepelumab is a fully human monoclonal antibody that binds directly to TSLP receptor (TSLP-R), reducing its stimulating activity on dendritic cells in response to TSLP [60].

Recent double-blind, randomised trials demonstrated a reduction in asthma exacerbations, improved lung function and asthma-related quality of life in patients receiving tezepelumab versus placebo [61, 62] with an adequate safety and tolerability profile in adults with severe, uncontrolled asthma [63, 64]. This molecule has been approved on 17 December 2021 by the FDA for clinical use in the United States [65].

Other targeted therapy

Several trials are underway to evaluate other biologic drugs targeting IL-33 or its ST2 receptor, which synergises with TSLP in promoting type-2 immune/inflammatory responses and induces airway hyper-responsiveness via the release of IL-13 from ILC2 and mast cells.

Itepekimab, a *new human monoclonal antibody against interleukin-33*, shows the efficacy in improving asthma control, quality of life and lung function in patients with moderate-to-severe asthma in a phase 2 randomised controlled trial [66].

Interleukin-23 has been associated with pathogenesis of asthma by promoting Th2 cytokine production and eosinophil infiltration [67]. Risankizumab, an anti-interleukine-23p19 antibody, failed to show efficacy in reducing asthma exacerbation compared to placebo in adults with severe asthma [68].

In asthma, expression of the prostaglandin D_2 receptor 2 (DP_2 receptor) is increased in the bronchial submucosa, and its ligand, prostaglandin D_2 is elevated in bronchoalveolar lavage. DP_2 receptor stimulation by prostaglandin D_2 mediates the activation and migration of some of the key inflammatory cell types in asthma, including T-helper-2 (Th2) cells, type 2 innate lymphoid cells, basophils, and eosinophils. It also stimulates type 2 cytokine release from these cells making it a potential new target for the treatment of asthma.

Fevipiprant, an oral antagonist of the prostaglandin D2 receptor 2, did not show results superior to placebo in the reduction of asthma exacerbations, improvement in lung function or other asthma-related clinical outcomes in recent randomized controlled trials [69].

Management of T2-Low and/or non-T2 asthma endotype

Compared to T2-high asthma, the underlying pathophysiological mechanisms in T2-low and/or non-T2 asthma are not completely understood. Presently, the suggested management involves lifestyle modifications such as smoking cessation and weight loss, as well as cessation of short-acting B-agonist use and utilisation of low-dose corticosteroid, long-acting muscarinic antagonists (LAMA), macrolides, and possibly bronchial thermoplasty [70].

Currently, no biological is approved for T2-low and/or non-T2 asthma, but several biological agents targeting IL-17 and other pathways are under investigation [70–75]. Recent RCT studies [76,77] suggested the efficacy of teze-

pelumab in reducing asthma exacerbations, independently of baseline bloods eosinophil counts (<250 cells/μL vs >250 cells/μL) and Th2 status (IgE >100 IU ml or less). It is therefore possible to speculate that, based on its wide upstream anti-inflammatory effects, tezepelumab may reduce asthma exacerbations equally in patients with different asthma phenotypes, including the T2-low asthma [60].

Management of severe asthma in children and adolescents: differences from adult guidelines

Asthma is still the most common chronic inflammatory airways disease in children and severe childhood asthma is associated with high morbidity and mortality. It thus represents a challenge for these children and adolescents, their families and the health care system [4].

Current guidelines provide appropriate management for mild to moderate asthma in the paediatric population but there is still a significant lack of research concerning the management in children and adolescent with severe asthma [7, 12].

Macrolides decrease the requirement for corticosteroids, improve asthma symptoms and reduce the rate of exacerbations in adults with severe asthma [78]. However, very few RCTs studied the role of macrolides in children and adolescents with asthma and failed to prove efficacy, most likely because of being insufficiently powered [79]. Therefore, thecurrent guidelines recommend against the utilisation of macrolides in the paediatric population with severe asthma [7, 12].

Children and adolescents present higher level of periostin than adults due to bone growth during puberty. Clinicians should therefore be cautious in interpreting serum periostin as a marker of asthma in children because normal ranges fluctuate among different age groups [80].

Presently, no evidence-based guidelines exist for the use of biologic therapy in children with severe uncontrolled asthma. Omalizumab and mepolizumab are approved for children ≥6 years old with moderate to severe asthma [7, 12].

Several randomised trials focused on the efficacy of benralizumab, reslizumab or dupilumab in severe T2-high asthma in 12 to 17 year olds. However, larger randomised controlled trials evaluating the safety and efficacy in children and adolescents with severe uncontrolled asthma are required to support specific evidence-based guidelines.

Conclusions

Severe asthma encompasses a small percentage of all patients with asthma, but represents an important disease burden with high mortality, morbidity, and costs. In the recent years, a major improvement in our understanding of underlying pathophysiological mechanisms, phenotypes and endotypes has revolutionised management of severe asthma with the development of specific biologic therapies.

T2-high asthma represents the majority of cases of severe uncontrolled asthma in adults and adolescents. It involves the activation of type 2 cytokines IL-4, IL-5, IL-13 and epithelial alarmins, such as TSLP, cytokines released by bronchial epithelial cells when exposed to various stimuli such as virus, bacteria, fungal products, smoke, and chemical environment.

Several randomised controlled trials have shown the efficacy and safety of new specific biological drugs targeting this T2-mediated inflammation in reducing asthma exacerbations, improving asthma related quality of life, symptom control and lung function. Based on the results of the NAVIGATOR study [63], tezepelumab is undergoing the approval process in Switzerland for treating T2-high and T2-low severe asthma. Moreover, other biotherapies against alarmins are in phase II trials [77, 81]. To date, there have been no head-to-head comparison of different biologics and trials have primarily focused on adult populations with insufficient data available in paediatric populations.

While it appears important to consider patients' characteristics, predictive biomarkers, phenotypes and endotypes to improve management of severe asthma, future research is crucial to understand pathophysiological mechanisms, particularly in T2-low and non-T2 asthma. More research is also needed to provide evidence-based strategies for novel therapeutic approaches in all age groups.

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