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LEADING ARTICLE

Targeted Therapy for Severe Asthma in Children and Adolescents: Current and Future Perspectives

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Abstract
Severe asthma in children remains a significant issue. It places a heavy burden on affected individuals and society as a whole in terms of high morbidity, mortality, consumption of healthcare resources, and side effects from high-dose corticosteroid therapy. New, targeted biologic therapies for asthma have emerged as effective add-on options, complementing our expanding understanding of asthma phenotypes/endotypes and the underlying immunopathology of the disease spectrum. They include omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. Omalizumab represents the first available therapeutic option for allergic asthma in patients as young as 6 years of age. Its efficacy and safety have been established by several randomized controlled trials specifically conducted in pediatric patients, leading to its final registration > 10 years ago. Three new interleukin (IL)-5 targeted agents, mepolizumab, reslizumab, and benralizumab, have been approved for the treatment of severe eosinophilic asthma starting from 6 years of age, and varying by country. More recently, dupilumab, a targeted agent against the IL-4 receptor α-chain, was approved for patients ≥12 years of age in the United States after pivotal trials were completed. The late-stage clinical testing of these targeted agents has mostly involved patients aged 12 years and up, and the application of those data to younger children can be inappropriate and carry risk. The efficacy and safety of these newer biologics in children should be supported by adequate research within this targeted age group. In this review, we will present the most recent evidence on these five biological therapies for severe asthma and will discuss dosage and administration, their efficacy, safety, and future prospects, with a focus on the pediatric age group, defined as age < 18 years.

1 Introduction

Severe asthma is a highly heterogeneous disorder with a reported prevalence of approximately 5% in children and 7% in adolescents [1]. Children with severe asthma experience troublesome persistent symptoms, neuropsychological problems [2], life-threatening acute attacks and side effects from high-dose oral corticosteroids (OCS) [3], accounting

Key Points

Encouraging findings from experimental and clinical studies have provided new insights into personalized biomarker-based targeted therapy for severe asthma.

Omalizumab was the first and, for a long time, the only biologic available as add-on therapy for uncontrolled allergic asthma in the pediatric population.

More recently, mepolizumab, benralizumab, and dupilumab have become available as subcutaneous injections for severe eosinophilic asthma in children older than 12 years of age.

Reslizumab is available as add-on therapy for the therapeutic management of patients with severe asthma aged ≥ 18 years and with eosinophilic phenotype.

More work is needed to clarify the ideal candidate, the optimal dosage, the duration of biological therapy, and its long-lasting effects after treatment discontinuation.

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for most of the morbidity and mortality caused by asthma and > 50% of the total health care costs attributable to asthma [3–5]. A multidisciplinary assessment is required for all children with suspected severe asthma [6]. The first critical step of this assessment is considering asthma-mimicking conditions in the differential diagnosis [6, 7]. Then, after evaluation of complicating comorbidities [8–10] and modifiable treatment-related issues, children with severe refractory asthma become candidates for additional biologic therapies.

Clinical phenotypes of pediatric severe asthma are characterized by an early onset and are usually associated with elevated levels of total serum immunoglobulin E (IgE), multiple aeroallergens sensitization, and raised blood eosinophils. Only a small subgroup of children presents with bronchial hyperresponsiveness and reduced lung function [11–13]. Each phenotype has been linked to different pathobiological mechanisms, frequently referred to as endotypes. At least two major endotypes of severe asthma have been proposed based on the type of airway inflammation: type 2 and non-type 2 [14]. Type 2 asthma is characterized by eosinophilic airway inflammation and allergic sensitization, being primarily driven by IgE, as well as key signature cytokines, such as interleukin (IL)-4, IL-5, and IL-13, released by cells of both the innate and adaptive immune system [15]. Although less common in children, non-type 2 asthma presents with either neutrophilic or paucigranulocytic airway inflammation sustained by IL-8, IL-17, IL-22, and other T cell-related cytokines, plus epithelial cell-derived cytokines [16, 17]. Currently, research efforts are focusing on the identification of noninvasive biomarkers able to predict treatment response and assist in designing personalized therapies for severe asthma [14, 18].

The shift from phenotype evaluation towards endotype analysis has enabled identification and application of patient-specific treatment in asthma management. With a more complete understanding of the inflammatory mediators involved in asthma, a number of new monoclonal antibodies have emerged, mainly targeting type 2 asthma. These are remarkable advances in our knowledge of severe asthma, but there are still unmet needs associated with its therapeutic management in the pediatric population [19].

In this review, we present the most recent evidence on biologic therapies for severe asthma and discuss their future perspective, focusing on the pediatric ages. To select relevant literature for inclusion in this review, we conducted a literature search using the PubMed database. The search using terms 'biologics OR biological agents', 'children OR adolescents' and 'severe asthma' yielded a total of 133 publications. Additional searches were conducted using the names of individual biologics, such as 'omalizumab' AND 'asthma.' The literature review was performed for publication years 2009–2019, restricting the articles to humans and English language publications. Potentially eligible publications were manually screened and reviewed, and nonrelevant publications were excluded.

2 Omalizumab

2.1 Dosage/Administration

The pharmacological blockade of IgE represents a successful strategy that has been applied to an array of therapeutic areas [20], including severe asthma, making for one of the greatest developments in the last 15 years [21]. Omalizumab is the first available humanized monoclonal anti-IgE with a pediatric indication (age ≥6 years) [22]. It is now recommended as add-on treatment for children with severe allergic asthma with elevated serum IgE (> 30 and < 1500 IU/mL) and positive specific IgE to at least one aeroallergen [6]. This therapy is recommended to be administered as a subcutaneous (SC) injection. The dose and frequency of dosing are guided by a nomogram derived from total serum IgE level and body weight in kilograms [22]. By binding to free IgE, omalizumab reduces cell-bound IgE, down-regulates IgE receptors, and prevents the release of pro-inflammatory mediators [23].

2.2 Efficacy

The efficacy and safety of omalizumab have been established by several randomized controlled trials specifically conducted in pediatric patients [24–27], leading to its final registration more than 10 years ago. Overall, omalizumab was effective in reducing the rate of asthma exacerbations, the number of hospitalizations for acute asthma attacks, and the related need of OCS in severe asthmatic children. These effects resulted in better asthma control and an improved quality of life (QoL) in children and their families [28]. Recent studies also reported a significant decrease in the number of seasonal exacerbations triggered by respiratory viruses in association with the restoration of antiviral defenses (in particular, type I interferon production) in treated subjects [25–27]. Moreover, real-life studies confirmed the effectiveness of omalizumab in children with severe asthma by demonstrating a significant improvement in asthma control, as well as a huge decrease in the number of severe exacerbations and hospitalizations [24, 29–32]. This impact was also observed in the discontinuation of daily OCS, the decrease of inhaled corticosteroids (ICS) dose, and a slight improvement in lung function [29–32].

2.3 Safety

A large amount of safety data from clinical trials and observational studies conducted in children and adolescents

showed that omalizumab is generally well tolerated [23, 28, 33–37]. In particular, omalizumab-associated anaphylaxis has a risk of occurring in 0.1–0.2% of adults and adolescents receiving this biologic agent, but it was not observed in pediatric studies [28, 33–35]. In observational studies, the main side effects reported were local (pain at the injection site, skin reactions), and had a short resolution [29–31]. Finally, there is no evidence to support an increased risk of malignancy in patients treated with omalizumab [35, 36], but long-term monitoring of treated patients is still required to confirm a good safety profile.

Data on clinical phenotypes and/or validated biomarkers predicting response to omalizumab treatment are still lacking and require further investigation. Age > 12 years [29], history of a recent asthma exacerbation and hospitalization in the past 6 months [27], and pre-bronchodilator forced expiratory volume in one second (FEV_1) < 90% of predicted [38] have been proposed as clinical characteristics associated with omalizumab efficacy. More recently, the best responding phenotype in children has been identified as severe asthma with multiple allergic comorbidities (such as multiple sensitizations, atopic dermatitis, and food allergy) associated with eosinophil counts of > 300 cells/μL, high levels of total IgE, and fractional exhaled nitric oxide (FeNO) [39, 40].

Much work is needed to better understand the value of omalizumab therapy in the pediatric asthma population. Relevant unmet needs are the current limit on omalizumab use in children younger than 6 years, in children with severe non-allergic asthma, and in children with total IgE > 1500 IU/mL. Preliminary positive results are available for non-allergic children [41], and for children with excessively high IgE levels [42]. A single study on uncontrolled asthmatic children aged < 6 years is ongoing (Preventing Asthma in High Risk Kids study, NCT02570984) with the goal of evaluating the disease-modifying effect of anti-IgE therapy [43]. The optimal duration of omalizumab therapy, as well as its long-lasting effect after suspension, are not yet clearly defined. The definition of targeted courses of therapy may represent the starting point for optimizing the cost effectiveness of this biologic treatment in the pediatric population.

3 Anti-Interleukin-5 (IL-5)

3.1 Mepolizumab

3.1.1 Dosage/Administration

Mepolizumab, a murine humanized immunoglobulin IgG1 monoclonal antibody acting against circulating IL-5, has recently been approved as add-on maintenance therapy for the treatment of severe eosinophilic asthma [44–46]. The indications for use of mepolizumab in clinical practice differ worldwide. The United States (US) Food and Drug Administration (FDA) [47] and the European Union [not the United Kingdom (UK)] [48] approved the use of mepolizumab as add-on treatment in asthmatic patients aged > 12 years with refractory disease, an eosinophilic phenotype (> 150 cells/μL), and a history of exacerbations (the number of exacerbations has not been stated). In contrast, the UK approved the use of mepolizumab in patients aged 6–11 years and adopted stricter criteria, including a blood eosinophil count of > 300 cells/μL once or more in the preceding 12 months, and requiring treatment with maintenance OCS and/or having a history of four or more exacerbations in the preceding year [49]. Currently, mepolizumab for SC use is available as a lyophilized powder in a single-dose glass vial for reconstitution, both as 100 mg for adults and children aged ≥ 12 years, and as 40 mg for children aged 6–11 years [44, 45].

No official treatment response criteria exist. Recently, Drick et al. proposed three clinical and laboratory criteria as predictors for treatment response in a real-life setting [50]. One adopted treatment response criterion was the patient-reported improvement of their condition with regard to symptoms, QoL, exacerbations, and physical fitness. In an adult population, the following thresholds should also be considered for mepolizumab therapy: (i) a blood eosinophil count ≥ 300 cells/μL; and (ii) a blood eosinophil count ≥ 150 cells/μL in patients with well characterized eosinophilic asthma or for subjects requiring regular OCS [51, 52]. More recently, improvement in FEV_1 has been adopted as a third response criterion [50].

The current guidelines did not establish when to discontinue mepolizumab. The National Institute for Health and Care Excellence (NICE) recommended that the decision to continue mepolizumab treatment is based on an assessment of at least a 50% reduction in exacerbation frequency at the end of 12 months of treatment [49]. Studies have highlighted that continued dosing is needed to maintain efficacy from mepolizumab therapy [53]. Patients who discontinued treatment after 12 months of therapy relapsed after 3–6 months of follow-up, showing a significant increase in the peripheral blood eosinophil count, in frequency of severe asthma exacerbations, and in the Asthma Control Questionnaire-5 (ACQ-5) score [54].

3.1.2 Efficacy

The efficacy and safety of mepolizumab in severe asthmatic patients with eosinophilic inflammation was assessed by Dose Ranging, Efficacy, and Safety with Mepolizumab in Severe Asthma (DREAM) [55] and by Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) [56]: two double-blind, randomized,

placebo-controlled studies in asthmatic patients ≥ 12 years of age. These studies reported a clinically significant decrease both in the number of asthma exacerbations [55, 56] and in asthma QoL score, especially in patients with a baseline blood eosinophil count of at least 500 cells/μL [55].

The Steroid Reduction with Mepolizumab (SIRIUS) study, enrolling 135 patients (age 16–74 years) receiving a high maintenance dose of ICS therapy, showed a 50% median reduction in OCS use and a significant clinical and lung function improvement when compared with the control group [51]. Combining MENSA and SIRIUS data, the COSMOS study, a 52-week, open-label extension trial, highlighted a durable and stable effect of mepolizumab over time, both in terms of exacerbation rate and OCS dosing. COSMOS also found an improvement in prebronchodilator FEV_1 and ACQ-5 [57] among mepolizumab users. The Long-Term Extension Safety Study of Mepolizumab in Asthmatic Subjects (COLUMBA) trial, an open-label extension of the DREAM study, assessed the long-term efficacy of mepolizumab, showing a significant reduction in exacerbation rates/year, changes from baseline in ACQ-5 score, and blood eosinophil counts [58].

3.1.3 Safety

In placebo-controlled trials, mepolizumab has demonstrated a favorable safety profile, appearing well tolerated [46, 51, 54, 56, 59]. The most commonly reported adverse events were injection-site reactions, respiratory infections, worsening of asthma [58], back pain, headaches, and fatigue [46, 51, 56].

Whether all of these findings strongly support the efficacy and safety of mepolizumab in the pediatric population is unknown, as to date, sufficient evidence is unavailable [53, 54]. Only 28 adolescents, aged 12–17 years old, have been enrolled in mepolizumab phase III studies [51, 55–58]. Moreover, just one study significantly contributed to the mepolizumab approval as an adjunctive treatment for severe refractory eosinophilic asthma in children aged 6–17 years, as it assessed the effectiveness of the therapy on exacerbation rate [60]. An event of histiocytic necrotizing lymphadenitis and one case of varicella infection have been reported in a pediatric population, but the association between mepolizumab and these two cases still remains uncertain [54]. Plans are underway, however, for more extensive study of mepolizumab in children. An open-label, pediatric pharmacokinetic and pharmacodynamics study and a safety and pharmacodynamics extension study, involving children aged 6–11 years, are slated to begin in September 2019 [61] (Table 1).

4 Reslizumab

4.1 Dosage/Administration

Reslizumab, an IgG4 kappa monoclonal antibody binding circulating IL-5, was approved in 2016 as add-on therapy for the therapeutic management of patients with severe asthma aged ≥ 18 years, and with eosinophilic phenotype [62]. In particular, the NICE Appraisal Committee recommended reslizumab as an option for treatment of inadequately controlled severe eosinophilic asthma despite maintenance therapy with high-dose ICS plus another drug, only when (i) blood eosinophil count is ≥ 400 cells/μL, (ii) the patient experienced three or more asthma exacerbations in the last year, and (iii) the company provides reslizumab at the agreed discount level in the patient access scheme [63]. The recommended reslizumab dosage is 3.0 mg/kg, administered once every 4 weeks as an intravenous (IV) infusion over 25–50 min [64].

4.2 Efficacy

The phase III BREATH clinical program, including four placebo-controlled efficacy and safety studies in patients with uncontrolled eosinophilic asthma on at least a medium-dose ICS and aged ≥ 12 years, showed a significant improvement in lung function, exacerbations, asthma symptoms, and asthma-related QoL in the reslizumab group versus placebo [65–67]. Also, a more significant clinical improvement was detected in patients with late- as compared with early-onset asthma [68]. Moreover, the initial improvement in lung function and asthma control, already reported at 2–3 days after the first dose of reslizumab [69], was maintained for up to 24 months [70]. Reslizumab has also been studied for its effect on reducing OCS use. A single-blind, placebo-controlled sequential trial revealed that reslizumab was effective in attenuating local and systemic eosinophilia, and in improving asthma control and FEV_1 [71].

To better identify 'responders' to reslizumab, Bateman et al. proposed a treatment algorithm based on (i) change from baseline in ACQ and Assessment of Quality of Life (AQoL), (ii) FEV_1, and (iii) numbers of exacerbations during the year before enrollment and the first 16 weeks of treatment. Unfortunately, this algorithm was not suitable for predicting unresponsive patients [72].

Incomplete data are available on the effect of stopping treatment, but it has been reported that eosinophil levels reverted to baseline by 4 months after discontinuing reslizumab treatment [70].

Efficacy of reslizumab in children has not been established. At the time of approval, reslizumab was not found to be effective in patients aged 12–17 years of age, as they

Table 1 Clinical development program for mepolizumab including pediatric population affected by asthma

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/ estimated study completion date	Safety[a]
A Trial of Mepolizumab Adjunctive Therapy for the Prevention of Asthma Exacerbations in Urban Children [NCT03292588]	Phase II (recruiting) *N*. pts = 320 Ages: 6–17 y Primary outcome measures: N. asthma exacerbations	Mepolizumab: 40 mg/4 wk for pts ages 6–11 y 100 mg/4 wk for pts ≥ 12 y of age Placebo	Not applicable September 2019	NR
Pharmacokinetics and Pharmacodynamics of Mepolizumab Administered Subcutaneously in Children [NCT02377427]	Phase II (completed) *N*. pts = 36 Ages: 6–11 y Primary outcome measures: maximum plasma concentration of mepolizumab	Mepolizumab: 40 mg/4 wk for pts ages 6–11 y 100 mg/4 wk for pts ≥ 12 y of age	Not applicable	All-cause mortality: 0/36 SAEs: Part A: Mepolizumab 40 mg: 11/26 (1 nausea, 2 chest pain, 2 infections and infestations, 3 back pain, 3 asthma) Mepolizumab 100 mg: 1/10 (1 LRTI) Part B: Mepolizumab 40 mg: 4/16 (1 anaphylactic shock, 2 asthma, 1 epistaxis) Mepolizumab 100 mg: 3/10 (1 pneumonia, 2 asthma) Mepolizumab 40/100 mg:1/10 (1 asthma) AEs: Part A: Mepolizumab 40 mg: 18/26 (9 GI disorders, 5 injection-site reaction, 1 pain, 1 pyrexia, 1 hypersensitivity, 18 infections and infestations, 1 ankle fracture, 1 body temperature increase, 1 neutrophil count decreased, 1 musculoskeletal pain, 5 NS disorders, 1 urinary retention, 10 respiratory, thoracic and mediastinal disorders, 2 cutaneous rash)[b] Mepolizumab 100 mg: 6/10 (1 vomiting, 6 infections and infestations, 1 GPT increased, 3 metabolism and nutrition disorders, 3 NS disorders)[b] Part B: Mepolizumab 40 mg: 15/16 (2 eye disorders, 6 GI disorders, 1 pyrexia, 1 adverse food reaction, 1 fatigue, 1 hepatic function abnormal, 1 seasonal allergy, 28 infections and infestations, 2 injury, poisoning and procedural complications, 1 neutrophil count decreased, 2 metabolism and nutrition disorders, 1 arthritis, 2 back pain, 4 NS disorders, 5 psychiatric disorders, 5 respiratory, thoracic and mediastinal disorders, 8 skin and subcutaneous tissue disorders, 1 orthostatic hypotension)[b] Mepolizumab 100 mg: 8/10 (1 lymphadenopathy, 1 eye swelling, 2 GI disorders, 1 pyrexia, 1 xerosis, 14 infections and infestations, 2 injury, poisoning and procedural complications, 1 joint swelling, 1 pain in extremity, 3 headache, 4 respiratory, thoracic and mediastinal disorders, 4 skin and subcutaneous tissue disorders)[b] Mepolizumab 40/100 mg: 4/4 (1 adrenal suppression, 2 GI disorders, 11 infections and infestations, 1 hyperglycemia, 2 NS disorders)[b]

Table 1 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/ estimated study completion date	Safety[a]
Study of Mepolizumab Safety Syringe in Asthmatics [NCT03021304]	Phase III (completed) *N*. pts = 56 Ages: 12–18 y Primary outcome measures: percentage of pts with successful self-administration of their observed third dose at week 8	Mepolizumab: 100 mg/4 wk	Not applicable	All-cause mortality: 0/56 SAEs: 3/56 (1 diverticulitis, 2 asthma) AEs: 4/56 (4 viral URTI)
Study of Mepolizumab Autoinjector in Asthmatics [NCT03099096]	Phase III (completed) *N*. pts = 159 Ages: 12–18 y Primary outcome measures: percentage of pts with successful self-administration of their observed third dose at week 8	Mepolizumab: 100 mg/4 wk	Not applicable	All-cause mortality: 0/159 SAEs: 3/159 (1 chest discomfort, 1 injury, poisoning and procedural complications, 1 respiratory, thoracic and mediastinal disorder) AEs: 27/159 (19 infections and infestations, 8 headache)
Cessation Versus Continuation of Long-term Mepolizumab in Severe Eosinophilic Asthma Patients [NCT02555371]	Phase III (recruiting) *N*. pts = 297 Ages: 12–18 y Primary outcome measures: time to first clinically significant exacerbation (worsening of asthma requiring use of systemic CS and/or hospitalization and/or ED visits)	Mepolizumab: 100 mg/4 wk Placebo	Not applicable July 2019	No results posted
A Safety and Efficacy Study of Mepolizumab in Subjects With Severe Asthma [NCT03562195]	Phase III (recruiting) *N*. pts = 300 Ages: 12–18 y Primary outcome measures: number of clinically significant exacerbations of asthma	Mepolizumab: 100 mg/4 weeks Placebo Salbutamol	Not applicable April 2021	No results posted

Table 1 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/ estimated study completion date	Safety[a]
A Phase IIIa, Repeat Dose, Open-label, Long-term Safety Study of Mepolizumab in Asthmatic Subjects [NCT02135692]	Phase III (completed) *N*. pts = 339 Ages: 12–18 y Primary outcome measures: annualized rate of on-treatment exacerbations per year N. of pts with any on-treatment AE or on-treatment SAE	Mepolizumab: 100 mg/4 wk Standard of care	Not applicable	All-cause mortality: 2/339 SAEs: 84/339 (6 cardiac disorders, 2 congenital, familial and genetic disorders, 8 GI disorders, 1 cyst, 3 immune system disorders, 32 infections and infestations, 13 injury, poisoning and procedural complications, 2 liver function test increased, 3 metabolism and nutrition disorders, 2 osteonecrosis, 1 arthritis, 1 back pain, 1 intervertebral disc protrusion, 1 musculoskeletal chest pain, 1 osteoarthritis, 1 pain in extremity, 1 polyarthritis, 1 rotator cuff syndrome, 5 neoplasms benign, malignant and unspecified, 3 NS disorders, 1 psychiatric disorder, 2 renal and urinary disorders, 1 reproductive system and breast disorders, 43 respiratory, thoracic and mediastinal disorders, 1 skin and subcutaneous tissue disorder, 1 vascular disorder)[b] AEs: 288/339 (56 GI disorders, 16 fatigue, 15 influenza-like illness, 15 injection-site reactions, 51 infections and infestations, 41 back pain, 32 arthralgia, 15 pain in extremity, 14 musculoskeletal pain, 11 myalgia, 72 NS disorders, 17 psychiatric disorders, 112 respiratory, thoracic and mediastinal disorders, 41 skin and subcutaneous tissue disorders, 14 vascular disorders)
Omalizumab to Mepolizumab Switch Study in Severe Eosinophilic Asthma Patients [NCT02654145]	Phase IV (completed) N. pts = 145 Ages: 12–18 y Primary outcome measures: Mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at week 32	Mepolizumab: 100 mg/4 wk Albuterol/salbutamol MDIs Omalizumab	Mepolizumab vs placebo: $p < 0.001$	All-cause mortality: 0/145 SAEs: 16/145 (1 cardiac disorders, 2 GI disorders, 1 chest discomfort, 1 hepatobiliary disorders, 7 infections and infestations, 3 NS disorders, 9 respiratory, thoracic and mediastinal disorders)[b] AEs: 107/145 (26 GI disorders, 20 fatigue, 8 asthenia, 10 chest pain, 23 injection-site reaction, 83 infections and infestations, 14 arthralgia, 13 back pain, 7 myalgia, 6 musculoskeletal pain, 6 neck pain, 46 NS disorders, 38 respiratory, thoracic and mediastinal disorders)
Mepolizumab Steroid-Sparing Study in Subjects With Severe Refractory Asthma [NCT01691508]	Phase III (completed) N. pts = 135 Ages: 12–18 y	Mepolizumab: 100 mg/4 wk Placebo	Mepolizumab vs placebo: $p = 0.008$	All-cause mortality: not stated SAEs: 1/69 (1 chronic sinusitis, 1 hypokalemia, 1 fistula)[b]

Table 1 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
	Primary outcome measures: percent reduction from baseline in OCS dose during wk 20–24 while maintaining asthma control	OCS (prednisone/prednisolone)		AEs: 47/69 (3 adrenal insufficiency, 5 GI disorders, 7 fatigue, 3 pyrexia, 4 injection-site reaction, 4 edema peripheral, 1 hypersensitivity, 42 infections and infestations, 2 injection-related reaction, 5 arthralgia, 4 pain in extremity, 2 back pain, 4 muscle spasms, 17 NS disorders, 3 insomnia, 4 oropharyngeal pain, 3 skin and subcutaneous tissue disorders)
Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Subjects With Severe Uncontrolled Refractory Asthma [NCT01691521]	Phase III (completed) N. pts = 580	Mepolizumab: 75 mg/4 wk IV 100 mg/4 wk SC	Mepolizumab vs placebo IV: $p < 0.001$	All-cause mortality: not stated SAEs: Mepolizumab 75 mg IV: 14/191 (1 GI disorder, 1 viral URTI, 3 injury, poisoning and procedural complications, 1 sciatica, 9 asthma, 1 angioedema)[b] Mepolizumab 100 mg SC 16/194 (1 congenital, familial and genetic disorders, 1 gallbladder disorder, 1 hypersensitivity, 7 infections and infestations, 1 inflammation of wound, 1 musculoskeletal chest pain, 2 renal and urinary disorders, 5 asthma, 1 dyshidrotic eczema)[b]
	Ages: 12 y and older Primary outcome measures: number of clinically significant exacerbations of asthma per year	Placebo	Mepolizumab vs placebo SC: $p < 0.001$	AEs: Mepolizumab 75 mg IV: 142/191 (17 GI disorders, 5 injection-site reaction, 8 fatigue, 6 hypersensitivity, 129 infections and infestations, 11 back pain, 10 arthralgia, 3 pain in extremity, 3 myalgia, 51 NS disorders, 42 respiratory, thoracic and mediastinal disorders, 2 eczema, 6 hypertension)[b] Mepolizumab 100 mg SC: 132/194 (30 GI disorders, 17 injection-site reaction, 5 fatigue, 2 hypersensitivity, 107 infections and infestations, 14 back pain, 11 arthralgia, 8 pain in extremity, 3 myalgia, 50 NS disorders, 30 respiratory, thoracic and mediastinal disorders, 9 eczema, 3 hypertension)[b]

Table 1 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma [NCT01000506]	Phase II (completed) N. pts = 621 Ages: 12–65 y Primary outcome measures: number of clinically significant exacerbations of asthma per year	Mepolizumab: 750 mg/4 wk 250 mg/4 wk 75 mg/4 wk Placebo	Mepolizumab 750 mg vs placebo IV: $p < 0.001$ Mepolizumab 250 mg vs placebo IV: $p < 0.001$ Mepolizumab 75 mg vs placebo IV: $p < 0.001$	All-cause mortality: not stated SAEs: Mepolizumab 75 mg: 20/153 (3 cardiac disorders, 1 chest pain, 7 infections and infestations, 1 injury, poisoning and procedural complications, 2 metabolism and nutrition disorders, 1 abortion spontaneous, 12 respiratory, thoracic and mediastinal disorders, 3 vascular disorders) Mepolizumab 250 mg: 24/152 (1 leukopenia, 1 coronary artery insufficiency, 3 GI disorders, 1 microlithiasis, 4 infections and infestations, 2 injury, poisoning and procedural complications, 1 reticulocyte count decreased, 1 uterine cancer, 2 renal and urinary disorders, 1 endometrial hyperplasia, 16 asthma, 1 distributive shock)[b] Mepolizumab 750 mg: 19/156: (4 cardiac disorders, 1 colitis, 6 infections and infestations, 1 tendon rupture, 1 cranial nerve disorder, 1 ovarian cyst, 10 respiratory, thoracic and mediastinal disorders, 1 hypertension)[b] AEs: Mepolizumab 75 mg: 113/15 (25 GI disorders, 5 edema peripheral, 6 fatigue, 1 chest pain, 5 injection-site reactions, 4 pyrexia, 4 asthenia, 2 hypersensitivity, 121 infections and infestations, 13 injury, poisoning and procedural complications, 11 back pain, 6 arthralgia, 5 pain in extremity, 2 myalgia, 3 musculoskeletal chest pain, 5 musculoskeletal pain, 3 tendonitis, 37 NS disorders, 136 infections and infestations, 9 injury, poisoning and procedural complications, 2 blood creatine phosphokinase increased, 35 musculoskeletal and connective tissue disorders, 36 NS disorders, 34 respiratory, thoracic and mediastinal disorders, 11 skin and subcutaneous tissue disorders, 6 hypertension)[b] Mepolizumab 250 mg: 113/152 (25 GI disorders, 6 edema peripheral, 7 fatigue, 7 chest pain, 4 pyrexia, 3 asthenia, 3 hypersensitivity, 121 infections and infestations, 13 injury, poisoning and procedural complications, 7 back pain, 9 arthralgia, 4 pain in extremity, 4 myalgia, 1 musculoskeletal pain, 4 tendonitis, 37 NS disorders, 47 respiratory, thoracic and mediastinal disorders, 9 skin and subcutaneous tissue disorders, 6 hypertension)[b] Mepolizumab 750 mg: 112/156 (33 GI disorders, 3 edema peripheral, 2 fatigue, 3 chest pain, 2 pyrexia, 3 hypersensitivity, 123 infections and infestations, 22 injury, poisoning and procedural complications, 5 blood creatine phosphokinase increased, 15 back pain, 9 arthralgia, 8 pain in extremity, 5 myalgia, 2 musculoskeletal chest pain, 2 musculoskeletal pain, 2 tendonitis, 40 NS disorders, 47 respiratory, thoracic and mediastinal disorders, 7 skin and subcutaneous tissue disorders, 4 hypertension)[b]

Table 1 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/ estimated study completion date	Safety[a]
Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Pts With Severe Eosinophilic Asthma on Markers of Asthma Control [NCT02281318]	Phase III (completed) *N*. pts = 556 Ages: 12 y and older Primary outcome measures: mean change from baseline (BL) in St. George's Respiratory Questionnaire (SGRQ) score at week 24	Mepolizumab: 100 mg/4 wk Standard of care Placebo	Mepolizumab vs placebo: $p < 0.001$	All-cause mortality: not stated SAEs: 15/273 (1 palpitations, 1 hiatus hernia, allergic granulomatous angiitis, 5 infections and infestations, 2 injury, poisoning and procedural complications, 1 blood glucose increased, 1 dizziness, 1 urethral stenosis, 4 respiratory, thoracic and mediastinal disorders, 1 subclavian vein thrombosis)[b]
A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects [NCT01842607]	Phase III (completed) *N*. pts = 651 Ages: 12 y and older Primary outcome measures: N. of pts with systemic AEs and local site reactions	Mepolizumab: 100 mg/4 wk	Not applicable	All-cause mortality: not stated SAEs: 94/651 (8 cardiac disorders, 1 ear and labyrinth disorder, 1 eye disorder, 8 GI disorders, 1 non-cardiac chest pain, 3 hepatobiliary disorders, 3 immune system disorders, 27 infections and infestations, 10 injury, poisoning and procedural complications, 1 ejection fraction decreased, 1 intervertebral disc protrusion, 1 musculoskeletal chest pain, 1 osteoarthritis, 1 spondylolisthesis, 1 vertebral foraminal stenosis, 5 neoplasms benign, malignant and unspecified, 4 NS disorders, 2 psychiatric disorders, 2 renal and urinary disorders, 11 reproductive system and breast disorders, 45 respiratory, thoracic and mediastinal disorders, 1 skin and subcutaneous tissue disorders, 2 vascular disorders) AEs: 461/651 (48 GI disorders, 29 injection-site reaction, 24 fatigue, 537 infections and infestations, 46 back pain, 44 arthralgia, 21 musculoskeletal pain, 21 pain in extremity, 87 headache, 121 respiratory, thoracic and mediastinal disorders)[b]

Adopted search strategy in clinicaltrials.gov: 'asthma' as condition or disease; 'mepolizumab' as other terms; 'recruiting' and/or 'completed' as status; 'child (birth–17)' as eligibility criteria

AEs adverse events, *CS* corticosteroids, *ED* emergency department, *GI* gastrointestinal, *GPT* glutamic pyruvic transaminase, *IV* intravenous, *LRTI* lower respiratory tract infections, *N* number, *NR* not reported, *NS* nervous system, *pts* participants, *SAEs* severe adverse events, *SC* subcutaneous, *URTI* upper respiratory tract infections

[a] Terms from vocabulary, MedDRA 20.1

[b] Patients experienced one or more adverse events

showed a decrease in lung function and an increase in exacerbation rates. In light of this evidence, studies in a pediatric population, ages 0–11 years, were waived [62].

4.3 Safety

Reslizumab appeared well tolerated in all patients, regardless of drug exposure time. Any increase in adverse events rate was recorded up to 36 months [69]. The most commonly reported adverse events were infections, worsening of asthma, and headache. No anaphylaxis cases have been described and the incidence of local infusion-related adverse events were rare. Changes in distribution of malignancies and mortality were not noted [70]. Despite these encouraging findings, the above-mentioned results are based on data from clinical trials rather than individual patients, so some confounding factors may be included. Also, the significant heterogeneity resulting from enrollment as well as bias in clinical trials design can lead to underestimating the adverse events rates. Consequently, studies are needed to improve drug safety, identify patients at high risk for adverse events, and improve monitoring of drug control strategies.

As for child safety data, the FDA Adverse Event Reporting System (FAERS) Search Strategy described a case of eosinophilic esophagitis and a case of chronic cholecystitis [62]. It is clear that evidence supporting reslizumab use in the pediatric population is lacking, so to fill this gap, a clinical development plan is currently underway (Table 2).

5 Benralizumab

5.1 Dosage/Administration

Benralizumab is a monoclonal antibody of murine origin binding the IL-5Rα, inducing a complete depletion of eosinophils, and modulating eosinophil-associated proteins and/or genes [73]. In the US, benralizumab was recently approved for add-on maintenance treatment of patients with severe eosinophilic asthma aged 12 years and older [74, 75]. In Europe, benralizumab is indicated for add-on maintenance treatment of adult patients with severe eosinophilic asthma that is inadequately controlled despite treatment with high-dosage ICS and long-acting β2-agonists (LABA) [74, 75]. The therapy is available as SC injection via a prefilled syringe, administered 30 mg every 4 weeks for the first three doses, and every 8 weeks thereafter [76].

5.2 Efficacy

Baseline clinical factors, such as blood eosinophils count ≥ 300 cells/mm^3, positive history of nasal polyposis, age at asthma diagnosis, pre-bronchodilator forced vital capacity (FVC), exacerbation frequency, and OCS use have been proposed to identify patients potentially responsive to benralizumab treatment [77, 78]. The SIROCCO and CALIMA studies, which were randomized, double-blind, parallel-group, placebo-controlled phase III trials, enrolled asthmatic patients aged 12–75 years with at least two exacerbations while on high-dosage ICS and LABA in the previous year. They showed a significant decrease in the annual asthma exacerbation rate and an improvement in prebronchodilator FEV_1 as well as in asthma symptoms in the benralizumab group as compared with placebo [79, 80]. A major therapeutic effect was detected in the group receiving therapy every 8 weeks versus the group treated every 4 weeks or with placebo [81]. In addition, the clinical response appeared greater in patients with higher baseline serum eosinophil levels [82]. These findings were not confirmed in the BISE (Benralizumab for patients with mild to moderate, persistent asthma) study, another phase III, randomized, parallel-group, placebo-controlled trial [83].

5.3 Safety

The BORA phase III extension trial, involving all patients previously enrolled in the SIROCCO, CALIMA, or ZONDA trials, was designed to assess the safety of the two dosing regimens of benralizumab over 56 weeks of treatment for adults, and over 108 weeks of treatment for adolescents [84]. The study reported similar results among the different treatment regimens and between patients who received 1 year versus 2 years of benralizumab [84]. Worsening of asthma appeared as one of the most frequently described severe adverse events in both benralizumab groups. Only 1–2% of patients experienced infections, suggesting that lower blood eosinophil levels due to treatment had no effect on susceptibility to infections. In 8–11% of patients receiving benralizumab for a second year, a positive anti-drug antibody response was detected, but it did not correlate with hypersensitivity or affect efficacy outcomes [85].

There has been no evidence to support a causal relationship between benralizumab, malignancies, and deaths in the asthma clinical studies [79–81, 83].

A safety extension study with benralizumab for asthmatic adults on ICS plus LABA (MELTEMI–NCT02808819), involving patients previously enrolled in the BORA trial, has an estimated completion date of June 2020 [86]. Other ongoing phase III trials are (i) study of the safety and effectiveness of benralizumab to treat patients with severe uncontrolled asthma (ANDHI), (ii) efficacy and safety study of benralizumab in patients with uncontrolled asthma on medium to high dose ICS plus LABA (MIRACLE), and (iii) a study to evaluate the onset of effect and time course of change in lung function with benralizumab in severe, uncontrolled asthma patients with eosinophilic inflammation

Table 2 Clinical development program for reslizumab including pediatric population affected by asthma

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
Study of Reslizumab in Patients With Uncontrolled Asthma and Elevated Blood Eosinophils [NCT02452190]	Phase III (completed) N. pts = 468 Ages: 12 y and older Primary outcome measures: frequency of clinical asthma exacerbations	Reslizumab: 110 mg/4 wk Placebo	Not applicable	Not applicable
A Study of Reslizumab in Patients 12 Years of Age and Older With Severe Eosinophilic Asthma [NCT03052725]	Phase III (completed) N. pts = 391 Ages: 12 y and older Primary outcome measures: frequency of AEs including SAEs	Reslizumab: 110 mg/4 wk	Not applicable	Not applicable
Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Reslizumab (3.0 mg/kg) as Treatment for Patients (12 Through 75 Years of Age) With Eosinophilic Asthma [NCT01290887]	Phase III (completed) *N.* pts = 1052 Ages: 12–75 y Primary outcome measures: participants with treatment-emergent adverse events	Reslizumab: 3.0 mg/kg/4 wk (±7 d)	Not applicable	All-cause mortality: not stated SAEs: 78/1051 (10 cardiac disorders, 1 amaurosis fugax, 5 GI disorders, 14 adverse drug reaction, 1 chest pain, 1 hernia, 1 suprapubic pain, 4 hepatobiliary disorders, 16 infections and infestations, 7 injury, poisoning and procedural complications, 1 liver function test abnormal, 2 metabolism and nutrition disorders, 12 neoplasms benign, malignant and unspecified, 3 NS disorders, 3 psychiatric disorders, 2 renal and urinary disorders, 1 reproductive system and breast disorders, 26 respiratory, thoracic and mediastinal disorders, 3 skin and subcutaneous tissue disorders, 3 vascular disorders) AEs: 519/1051 (396 infections and infestations, 73 headache, 301 asthma)[b]
A Study to Evaluate the Efficacy and Safety of Reslizumab in Patients With Eosinophilic Asthma [NCT01285323]	Phase III (completed) *N.* pts = 464 Ages: 12–75 y Primary outcome measures: frequency of CAEs (worsening of asthma requiring use of systemic corticosteroids and/or hospitalization and/or ED visits) during 12 months of treatment	Reslizumab: 3.0 mg/kg/4 wk Placebo	Reslizumab vs placebo: $p < 0.0001$	All-cause mortality: not stated SAEs: 18/232 (1 inguinal hernia, 2 anaphylactic reaction, 8 infections and infestations, 7 injury, poisoning and procedural complications, 1 back pain, 1 foot deformity, 1 plasmacytoma, 10 respiratory, thoracic and mediastinal disorders)[b] AEs: 123/232 (55 infections and infestations, 12 back pain, 33 headache, 66 asthma)[b]

Table 2 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
A Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12–75 Years of Age) With Eosinophilic Asthma [NCT01287039]	Phase III (completed) *N.* pts = 489 Ages: 12–75 y Primary outcome measures: frequency of clinical asthma exacerbations (CAEs) during 12 months of treatment	Reslizumab: 3.0 mg/kg/4 wk Placebo	Reslizumab vs placebo: $p < 0.0001$	All-cause mortality: not stated SAEs: 24/245 (3 GI disorders, 2 chest pain, 4 infections and infestations, 6 injury, poisoning and procedural complications, 1 metabolism and nutrition disorders, 4 neoplasms benign, malignant and unspecified, 11 asthma, 1 deep vein thrombosis)[b] AEs: 165/245 (141 infections and infestations, 13 back pain, 24 NS disorders, 129 respiratory, thoracic and mediastinal disorders)[b]
A Study to Evaluate the Efficacy and Safety of Reslizumab (0.3 or 3.0 mg/kg) as Treatment for Patients (12–75 Years of Age) With Eosinophilic Asthma [NCT01270464]	Phase III (completed) *N.* pts = 315 Ages: 12–75 y Primary outcome measures: change from baseline in FEV_1 over 16 weeks using mixed model for repeated measures	Reslizumab: 3.0 mg/kg/4 wk 0.3 mg/kg/4 wk Placebo	Reslizumab 3.0 mg/kg vs placebo: $p = 0.0018$ Reslizumab 0.3 mg/kg vs placebo: $p = 0.0237$	All-cause mortality: not stated SAEs: Reslizumab 0.3 mg/kg: 0/103 Reslizumab 3.0 mg/kg: 4/103 (2 infections and infestations, 2 injury, poisoning and procedural complications, 3 asthma) AEs: Reslizumab 0.3 mg/kg: 20/103 (6 nasopharyngitis, 8 headache, 6 asthma) Reslizumab 3.0 mg/kg: 28/103 (6 nasopharyngitis, 11 headache, 14 asthma)[b]
An Efficacy and Safety Study of Reslizumab Subcutaneous in Patients With Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils [NCT02501629]	Phase III (completed) *N.* pts = 177 Ages: 12 y and older Primary outcome measures: *N* of participants with reduction in daily OCS (defined as the 5-level categorized percent reduction in OCS dose during weeks 20–24 compared with the optimized dose at baseline)	Reslizumab: 110 mg/4 wk Placebo Non-OCS OCS	Reslizumab vs placebo: $p = 0.468$	All-cause mortality: 1/88 SAEs: 10/88 (1 inguinal hernia, 1 sudden death, 1 drug hypersensitivity, 3 infections and infestations, 1 syncope, 3 asthma) AEs: 20/88 (18 infections and infestations, 5 asthma, 1 hypertension)[b]

Adopted search strategy in clinicaltrials.gov: 'asthma' as condition or disease; 'reslizumab' as other terms; 'recruiting' and/or 'completed' as status; 'child (birth–17)' as eligibility criteria

AEs adverse events, *CAEs* clinical asthma exacerbations, *ED* emergency department, *FEV_1* forced expiratory volume in one second, *GI* gastrointestinal, *N* number, *NS* nervous system, *OCS* oral corticosteroids, *pts* participants, *SAEs* severe adverse events

[a]Terms from vocabulary, MedDRA 20.1

[b]Patients experienced one or more adverse events

Table 3 Clinical development program for benralizumab including pediatric population affected by asthma

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
Study to Evaluate the Potential Effect of Benralizumab on the Humoral Immune Response to the Seasonal Influenza Vaccination in Adolescent and Young Adult Patients With Severe Asthma [NCT02814643]	Phase III (completed) *N*. pts = 103 Ages: 12–21 y Primary outcome measures: 1. Postdose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rise from week 8 to week 12 2. Postdose strain-specific hemagglutination-inhibition antibody geometric mean titer obtained at week 12 3. Proportion of patients who experienced a strain-specific postdose antibody response at week 12 with antibody response Proportion of patients who achieved a strain-specific postdose hemagglutination inhibition antibody titer ≥ 40 at week 12	Benralizumab: 1 mL/4 wk Placebo Seasonal influenza virus vaccine	Not applicable	All-cause mortality: 0/51 SAEs; 0/51 AEs: 28/51 (3 GI disorders, 13 infections and infestations, 2 ligament sprain, 3 costochondritis, 3 headache, 9 respiratory, thoracic and mediastinal disorders, 1 acne)[b]
Efficacy and Safety Study of Benralizumab in Patients With Uncontrolled Asthma on Medium to High Dose Inhaled Corticosteroid Plus LABA (MIRACLE) [NCT03186209]	Phase III (recruiting) *N*. pts = 666 Ages: 12–75 y Primary outcome measures: annual asthma exacerbation rate in patients with uncontrolled asthma on medium- to high-dose ICS–LABA	Benralizumab: 30-mg dose Placebo	Not applicable February 2021	Not applicable

Table 3 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
Efficacy and Safety Study of Benralizumab Added to High-Dose Inhaled Corticosteroid Plus LABA in Patients With Uncontrolled Asthma [NCT01928771]	Phase III (completed) *N*. pts = 2681 Ages: 12–75 y Primary outcome measures: annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma for eosinophils ≥ 300/uL	Benralizumab:30-mg dose 4 wk 30-mg dose 8 wk Placebo	Benralizumab 30-mg dose 4 wk vs placebo: $p < 0.001$ Benralizumab 30-mg dose 8 wk vs placebo: $p < 0.001$	All-cause mortality: not stated SAEs: Benralizumab 30-mg dose 4 wk: 51/403 (2 cardiac disorders, 2 eye disorders, 2 GI disorders, 1 edema peripheral, 2 cholecystitis acute, 1 allergic granulomatous angiitis, 6 infections and infestations, 3 injury, poisoning and procedural complications, 1 foot deformity, 1intervertebral disc degeneration, 1 osteoarthritis, 1 ovarian epithelial cancer, 3 NS disorders, 1 panic attack, 1 nephrolithiasis, 1 endometriosis, 27 respiratory, thoracic and mediastinal disorders, 2 skin and subcutaneous tissue disorders) Benralizumab 30-mg dose 8 wk: 54/394 (1 hypercoagulation, 2 cardiac disorders, 1 goiter, 4 GI disorders, 1 chest pain, 1 sudden death, 1 cholecystitis, 12 infections and infestations, 6 injury, poisoning and procedural complications, 1 diabetes mellitus, 1 vertebral foraminal stenosis, 3 neoplasms benign, malignant and unspecified, 1 cerebral venous thrombosis, 1 abortion spontaneous, 1 renal failure, 24 asthma, 2 skin and subcutaneous tissue disorders, 2 hypertension)[b] AEs: Benralizumab 30-mg dose 4 wk: 214/403 (8 nausea, 16 pyrexia, 205 infections and infestations, 11 arthralgia, 12 back pain, 3 pain in extremity, 31 headache, 74 respiratory, thoracic and mediastinal disorders)[b] Benralizumab 30-mg dose 8 wk: 199/394 (12 nausea, 12 pyrexia, 197 infections and infestations, 18 arthralgia, 8 back pain, 13 pain in extremity, 37 headache, 52 respiratory, thoracic and mediastinal disorders)[b]

Table 3 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
A Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab (MEDI-563) in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus LABA (BORA) [NCT02258542]	Phase III (completed) *N.* pts = 2133 Ages: 12–75 y Primary outcome measures: number of adolescent patients with adverse events/abnormal lab variables, physical examinations as measures of safety and tolerability of two dosing regimens of benralizumab for adolescent patients	Benralizumab: not applicable	Not applicable	Not applicable
Efficacy and Safety Study of Benralizumab in Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist [NCT01914757]	Phase III (completed) *N.* pts = 2508 Ages: 12–75 y Primary outcome measures: annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma for patients with baseline eosinophils ≥ 300/uL	Benralizumab: 30-mg dose 4 wk 30-mg dose 8 wk Placebo	Benralizumab 30 mg dose 4 wk vs placebo: $p = 0.002$ Benralizumab 30 mg dose 8 wk vs placebo: $p = 0.019$	All-cause mortality: not stated SAEs: Benralizumab 30-mg dose 4 weeks: 46/438 (3 cardiac disorders, 2 GI disorders, 1 chest pain, 3 hepatobiliary disorders, 9 infections and infestations, 1 road traffic accident complications, 1 intervertebral disc disorder, 1 jaw cyst, 1 muscular weakness, 1 osteoarthritis, 1 rheumatoid arthritis, 1 spinal osteoarthritis, 3 neoplasms benign, malignant and unspecified, 1 syncope, 1 completed suicide, 3 renal and urinary disorders, 23 respiratory, thoracic and mediastinal disorders, 1 urticaria, 1 hypertensive crisis)[b] Benralizumab 30-mg dose 8 wk: 41/428 (3 cardiac disorders, 1 cataract, 1 gastroduodenitis, 1 chest pain, 1 death, 1 cholecystitis, 2 immune system disorders, 9 infections and infestations, 4 injury, poisoning and procedural complications, 1 obesity, 1 back pain, 1 Dupuytren's contracture, 1 osteoarthritis, 1 colon neoplasm, 2 NS disorders, 1 depression, 19 asthma, 1urticaria papular, 1 hypertension)[b] AEs: Benralizumab 30-mg dose 4 wk: 244/438 (16 pyrexia, 241 infections and infestations, 8 arthralgia, 17 back pain, 33 headache, 81 respiratory, thoracic and mediastinal disorders, 12 hypertension)[b] Benralizumab 30-mg dose 8 wk: 232/428 (13 pyrexia, 230 infections and infestations, 14 arthralgia, 11 back pain, 34 headache, 62 respiratory, thoracic and mediastinal disorders, 18 hypertension)[b]

Table 3 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
FASENRA SCEI for Long-Term Use [NCT03588546]	Phase not applicable (recruiting) *N*. pts = 780 Ages: child, adult, older adult Primary outcome measures: incidences of adverse drug reactions (ADRs)	Benralizumab: 30 mg	April 2025	Not applicable

Adopted search strategy in clinicaltrials.gov: 'asthma' as condition or disease; 'benralizumab' as other terms; 'recruiting' and/or 'completed' as status; 'child (birth–17)' as eligibility criteria

AEs adverse events, *GI* gastrointestinal, *ICS* inhaled corticosteroid, *LABA* long-acting β2 agonist, *N* number, *NS* nervous system, *pts* participants, *SAEs* severe adverse events

[a]Term from vocabulary, MedDRA 20.1

[b]Patients experienced one or more adverse events

(SOLANA). In addition, to assess the effects of benralizumab on asthma exacerbations, lung function, and QoL, the ANDHI trial (NCT03170271) aims to investigate the impact of benralizumab on comorbidities of asthma, including chronic rhinosinusitis and nasal polyposis [87]. The primary outcome of the MIRACLE trial (NCT03186209) is to assess, in severe asthmatics receiving medium-to-high doses of ICS/LABA medications, the ability of benralizumab to affect the asthma exacerbations per year [88]. Last, SOLANA (NCT02869438) is also studying the impact of benralizumab on symptom score, QoL, lung function, and serum eosinophils levels [89].

A summary of ongoing benralizumab studies in pediatric patients with eosinophilic asthma appears in Table 3.

6 Dupilumab

6.1 Dosage/Administration

Dupilumab is a fully human IgG4 monoclonal antibody, which acts by blocking the signal transduction network mediated by IL-4 and IL-13 [90]. In March 2017, dupilumab was approved in the US for adolescents aged ≥ 12 years, and in adults with moderate-to-severe asthma and eosinophilia (≥ 300 cells/μL) [91]. Dupilumab is available by SC injection via a prefilled syringe, administered 400 mg once, then 200 mg every 2 weeks, or 600 mg once, then 300 mg every 2 weeks [91].

6.1.1 Efficacy and Safety

Two large, well performed, randomized, double-blind, placebo-controlled, parallel-group phase III studies evaluated the efficacy and safety of dupilumab in patients with persistent asthma [92, 93]. The QUEST trial, enrolling 1902 patients > 12 years of age with uncontrolled, moderate-to-severe asthma despite daily ICS therapy, showed that dupilumab significantly reduced the annualized rate of severe asthma exacerbations ($p < 0.0001$). This major effect was observed in those patients showing higher baseline blood eosinophil count (> 300 cells/mm^3) and FeNO > 25 ppb. These positive findings were maintained for the 52-week treatment period for both dupilumab dosings [92].

In evaluating dupilumab in patients with severe steroid dependent asthma (VENTURE trial) [93], dupilumab treatment reduced OCS use while significantly improving FEV_1 and reducing the rate of severe exacerbations. Both QUEST and VENTURE trials also reported a transient eosinophilia in the dupilumab group as compared with placebo, not correlating with clinical adverse events [92–94]. Apart from injection-site reactions with dupilumab, there were no

Table 4 Clinical development program for dupilumab including pediatric population affected by asthma

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
Continuation of TRAVERSE-LTS12551 Evaluating Dupilumab Safety in Patients With Asthma (Long-Term Follow-Up) [NCT03620747]	Phase III (recruiting) *N*. pts = 750 Ages: 12 y and older Primary outcome measures: treatment-emergent adverse events	Dupilumab: One dose administered every 2 wk	Not applicable September 2021	Not applicable
Assessment of the Safety and Efficacy of Dupilumab in Children With Asthma (Liberty Asthma Excursion [NCT03560466]	Phase III (recruiting) *N*. pts = 377 Ages: 7–12 y Primary outcome measures: treatment-emergent adverse events	Dupilumab: Doses of dupilumab will be administered every 2 wk for 52 wk Asthma controller therapies Asthma reliever therapies	Not applicable April 2026	Not applicable
Evaluation of Dupilumab in Children With Uncontrolled Asthma (VOYAGE) [NCT02948959]	Phase III (recruiting) *N*. pts = 471 Ages: 6–12 y Primary outcome measures: annualized rate of severe exacerbation events during the placebo-controlled treatment period	Dupilumab: Doses will be administered every 2 wk Asthma controller therapies Asthma reliever therapies	Not applicable July 2021	Not applicable
Evaluation of Dupilumab in Patients With Severe Steroid Dependent Asthma (VENTURE) [NCT02528214]	Phase III (completed) *N*. pts = 210 Ages: 12 y and older Primary outcome measures: percentage reduction from baseline in oral corticosteroids dose at week 24 while maintaining asthma control	Dupilumab: 300 mg/2 wk Placebo Oral corticosteroid therapy	Dupilumab vs placebo $p < 0.0001$	All-cause mortality: 0/103 SAEs: 9/103 (2 eosinophilia, 2 infections and infestations, 2 injury, poisoning and procedural complications, 7 respiratory, thoracic and mediastinal disorders)[b] AEs: 23/103 (16 infections and infestations, 7 eosinophil count increased)

Table 4 (continued)

Study title	Study design and characteristics	Interventions and drugs	Preliminary results/estimated study completion date	Safety[a]
Evaluation of Dupilumab in Patients With Persistent Asthma (Liberty Asthma Quest) [NCT02414854]	Phase III (completed) *N*. pts = 1902 Ages: 12 y and older Primary outcome measures: 1. Annualized rate of severe exacerbation events during the 52-week treatment period 2. Absolute change from baseline in pre-bronchodilator FEV_1 at week 12	Dupilumab: 200 mg/2 wk 300 mg/2 wk Placebo Inhaled corticosteroid therapy	Dupilumab vs placebo $p < 0.0001$	All-cause mortality: 1. Dupilumab 200 mg/2 wk: 1/631 2. Dupilumab 300 mg/2 wk: 5/632 SAEs: Dupilumab 200 mg/2 wk: 51/631 (4 cardiac disorders, 1 congenital, familial and genetic disorders, 7 GI disorders, 1 chest pain, 2 hepatobiliary disorders, 2 immune system disorders, 5 infections and infestations, 3 injury, poisoning and procedural complication, 2 alanine aminotransferase increased, 1 costochondritis, 1 myalgia, 1 polychondritis, 8 neoplasms benign, malignant and unspecified, 4 NS disorders, 1 product issues, 2 psychiatric disorders, 1 renal infarct, 1 ovarian cyst, 16 respiratory, thoracic and mediastinal disorders, 2 social circumstances, 1 hypertension)[b] Dupilumab 300 mg/2 wk: 56/632 (1 eosinophilia, 10 cardiac disorders, 2 eye disorders, 6 GI disorders, 1 chest pain, 1 impaired healing, 1 injection-site erythema, 1 injection-site inflammation, 1 injection-site edema, 4 hepatobiliary disorders, 1 anaphylactic reaction, 14 infections and infestations, 10 injury, poisoning and procedural complications, 1 musculoskeletal chest pain, osteoarthritis, 1 pathological fracture, 5 neoplasms benign, malignant and unspecified, 2 NS disorders, 1 pregnancy, puerperium and perinatal conditions, 2 psychiatric disorders, 1 urinary incontinence, 1 cervical cyst, 13 respiratory, thoracic and mediastinal disorders, 1 thrombophlebitis superficial)[b] AEs: Dupilumab 200 mg/2 wk: 363/631 (76 injection-site erythema, 23 injection-site edema, 353 infections and infestations, 31 accidental overdose, 30 back pain, 47 headache, 21 rhinitis allergic)[b] Dupilumab 300 mg/2 wk: 378/632 (98 injection-site erythema, 40 injection-site edema, 343 infections and infestations, 34 accidental overdose, 25 back pain, 40 headache, 18 rhinitis allergic)[b]

Adopted search strategy in clinicaltrials.gov: 'asthma' as condition or disease; 'dupilumab' as other terms; 'recruiting' and/or 'completed' as status; 'child (birth–17)' as eligibility criteria

AEs adverse events, *CAEs* clinical asthma exacerbations, *ED* emergency department, FEV_1 forced expiratory volume in one second, *GI* gastrointestinal, *LABA* long-acting β2 agonist, *N* number, *NS* nervous system, *OCS* oral corticosteroids, *pts* participants, *SAEs* severe adverse events

[a]Terms from vocabulary, MedDRA 20.1

[b]Patients experienced one or more adverse events

significant differences between the two groups in the development of any adverse event.

Evidence of dupilumab in the pediatric population with uncontrolled asthma is still not available. Results are anticipated from the ongoing VOYAGE trial (NCT02948959) [95], a randomized, double-blind, placebo-controlled, parallel-group, phase III study enrolling children 6–12 years of age (Table 4).

7 Future Perspectives

Current research efforts are directed at clarifying some limitations regarding available biologic therapies. Specific and significant evidence of effectiveness and safety are lacking in the pediatric population since trials of the newly approved ones, such as anti-IL-5 and IL-4, have included only limited numbers of patients younger than 18 years. Moreover, direct comparison of these therapies is needed to make targeted treatment decisions and reduce related healthcare costs. Validated and available biomarkers of asthma endotypes should be incorporated into shared therapeutic algorithms to improve patient selection. Since the duration of these treatments is not clear, many patients are continued to long term. Additional large studies looking at patients who discontinue biological therapies after years of treatment are needed in the pediatric population to assess a possible long-lasting effect on asthma control and to monitor possible adverse effects, even long after discontinuing treatment.

New biologic therapies targeting upstream cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), involved in both T2 high and low asthma endotypes, are in various stages of clinical development. None of these therapies is currently being investigated in childhood. Moreover, new delivery techniques for biologic agents (i.e., by nebulizing) are under investigation with the aim of replacing injections, improving effectiveness and patients' compliance, and limiting systemic side effects. Finally, it is not clear whether these biologic agents have a modifying effect on the asthma process. If so, their indications could be extended earlier to most of the asthmatic population, and the therapeutic scenario would indeed be revolutionized.

8 Conclusion

As childhood asthma is commonly type-2 driven, monoclonal antibodies modulating the Th_2 cells activation and/or their proinflammatory effectors appear to be the most promising emerging therapeutic strategies. While the efficacy and safety of omalizumab have been extensively demonstrated in several pediatric clinical drug trials and real-world studies, the approval of other biologics in pediatric populations is mainly based on data generated in adults. Even though the clinical development plan in children is ongoing, extrapolating data obtained from adults to children can be inappropriate and is not risk-free. Moreover, as they are licensed for chronic treatment, little is known about the long-term effects of these biologic drugs, especially on developing children. The efficacy and safety of biologics in children need to be supported by adequate research within the targeted age group, and the analysis data from post-marketing use, including studies from registries and phase IV clinical trials, might prove crucial in optimizing the program development for biologics in this population.

Compliance with Ethical Standards

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Conflict of interest Amelia Licari, Sara Manti, Riccardo Castagnoli, Giuseppe Fabio Parisi, Carmelo Salpietro, Salvatore Leonardi, and Gian Luigi Marseglia have no conflicts of interest that are directly relevant to the content of this study.

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