

Biologics to Treat Severe Asthma in Children and Adolescents: A Practical Update

Gian Luigi Marseglia, MD,¹ Amelia Licari, PhD,¹ Maria Angela Tosca, PhD, PhD,² and Giorgio Ciprandi, MD³

Background: Severe asthma represents a significant challenge for children and adolescents. At the same time, it often places a burden on patients, caregivers, and society, mainly related to morbidity, mortality, and health care resources. In children and adolescents, severe asthma is mostly characterized by type 2 inflammation, which leads to bronchial eosinophilia that may be suppressed by corticosteroids. However, in this age group, a high dosage of inhaled corticosteroids combined with systemic corticosteroids sometimes results in unacceptable side effects, such as reduced growth velocity and reduced bone mineral density. Therefore, there is increasing and enthusiastic interest in today's biologics, including omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. There is growing evidence that they may be effective and safe add-on options for children and adolescents.

In 2009, omalizumab was approved by the European Medicines Agency as the first available therapeutic option for allergic asthma in patients as young as 6 years of age, followed by a similar approval by the U.S. Food and Drug Administration in 2016. Previously, omalizumab was marketed for this indication in patients $\geq$ age 12. Subsequent biologics, namely mepolizumab, reslizumab, and benralizumab, are IL-5 targeted agents that are presently approved in some countries for severe eosinophilic asthma starting at 6 years of age. Dupilumab is targeted against the IL-4 receptor α -chain, and it has been approved in the United States and the European Union as an add-on maintenance therapy in patients ≥ 12 years of age.

Conclusion: This review presents the most recent evidence on approved biologics for the treatment of severe asthma and discusses the unmet needs and future perspective, focusing on the pediatric and adolescent age groups.

Keywords: severe asthma, biologics, allergy, type 2 inflammation, eosinophils, children, adolescents

Introduction

SEVERE ASTHMA APPROXIMATELY affects 5% of children with asthma and 7% of adolescents with asthma.¹ Children with severe asthma represent a heterogeneous group of patients that can vary widely in clinical presentation, severity, and pathobiology.¹ The International European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines define severe asthma as inadequate control of asthma under high-intensity treatment with inhaled corticosteroids (ICS) and additional controllers, including oral corticosteroid (OCS), for at least 6 months per year, or by loss of asthma control on the attempt to reduce the high-intensity treatment.² In patients with severe asthma, differential diagnosis of asthma should be considered, comorbidities should be treated, persistent triggers should be eliminated, and patient adherence should be assessed.^{3,4} This approach helps to identify the subtended im-

munopathological characteristics of the two main currently recognized phenotypes: type 2 and non-type 2.^{5,6}

From a clinical perspective, children and adolescents with severe asthma usually experience troublesome and persistent symptoms up to life-threatening acute attacks. They may have emotional problems, including anxiety and depression, frequently present in caregivers.⁷ Children and adolescents may also present side effects due to high-dose OCS.⁸ This wide-ranging impact accounts for most of the morbidity and mortality caused by asthma and >50% of the total health care costs attributable to asthma.⁸⁻¹⁰ Therefore, the workup of severe asthma requires a multidisciplinary approach¹ that helps asthma-mimicking conditions and comorbidities to be immediately excluded.

Pediatric severe asthma phenotypes are usually characterized by an early onset and association with elevated levels of total serum immunoglobulin E (IgE), poly-sensitization,

¹Department of Pediatrics, Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy.

²Pediatric Allergy Center, Istituto Giannina Gaslini, Genoa, Italy.

³Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy.

and eosinophilia. Surprisingly, bronchial obstruction and hyperresponsiveness are documented in only a small subgroup of children and adolescents with severe asthma.^{11–13}

Airway inflammation is commonplace in severe asthma, and may be subdivided into type 2, and non-type 2 phenotypes.¹⁴ Type 2 asthma is characterized by eosinophilic airway inflammation and sensitization, such as IgE-mediated, T helper 2 (Th2)-dependent cytokines, including interleukin (IL)-4, IL-5, and IL-13.¹⁵ The non-type 2 asthma is uncommon in children and adolescents, and it is characterized by either neutrophilic or pauci-granulocytic airway infiltrate, promoted by IL-8, IL-17, IL-22, and epithelial cell-derived cytokines.^{16–19}

To better understand asthma, it has been divided into multiple phenotypes and endotypes. By definition, phenotype is “the visible characteristics of an organism resulting from the interaction between its genetic makeup and the environment.” Endotype refers to “a subtype of a condition, which is defined by a distinct functional or pathophysiological mechanism.”¹ Conceptually, moving from phenotyping to endotyping has allowed us to identify and tailor personalized treatment in asthma management. This

framework is useful with the emergence of new monoclonal antibodies that mainly target type 2 asthma.²⁰ This article details the principal characteristics of these biologics, including omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab (Table 1).

Omalizumab

The opportunity to block IgE was viewed as an attractive therapeutic approach in allergy, particularly asthma.^{21–23} Omalizumab is a humanized monoclonal anti-IgE and received a pediatric indication from the Food and Drug Administration (FDA) in 2016²⁴ for an add-on treatment for children $\geq$ age six but $<$ age 12 with severe allergic asthma with elevated serum IgE ($>$ 30 and $<$ 1500 IU/mL) and positive specific IgE to at least one perennial aeroallergen. This approval followed the European Medicines Agency (EMA) authorization in 2009 for children with severe persistent allergic asthma in this same age group.²⁵ Omalizumab is administered subcutaneously every 2–4 weeks and dosing is calculated based on body weight and total serum IgE at baseline. This biologic

TABLE 1. BIOLOGICALS APPROVED FOR THE TREATMENT OF SEVERE ASTHMA

<i>Biologic</i>	<i>Target</i>	<i>Indication</i>	<i>Dosage and administration route</i>	<i>Outcomes</i>
Omalizumab	IgE	Moderate to severe allergic asthma in patients $\geq$ 6 years of age (US, EU)	75–600 mg SC q2–4 wk based on IgE and wt	↓ Asthma exacerbations, ↓ asthma symptoms, ↑ FEV ₁ , ↑ QoL, ↓ ICS dose, ↓ seasonal exacerbations
Mepolizumab	IL-5	Severe eosinophilic asthma in patients aged $\geq$ 6 years of age (US, EU)	100 mg SC q4 wk	↓ Asthma exacerbations, ↓ asthma symptoms, ↑ FEV ₁ , ↑ QoL, ↓ ICS dose
Reslizumab	IL-5	Severe eosinophilic asthma in patients aged $\geq$ 18 years of age (US, EU)	3 mg/kg IV q4 wk	↓ Asthma exacerbations, ↓ asthma symptoms, ↑ FEV ₁ , ↑ QoL, ↓ ICS dose
Benralizumab	IL-5 receptor alpha	Severe eosinophilic asthma in patients $\geq$ 12 years of age (US)	30 mg SC q4 wk for the first 3 doses followed by 30 mg q8 wk	↓ Asthma exacerbations, ↓ asthma symptoms, ↑ FEV ₁ , ↑ QoL, ↓ ICS dose
Dupilumab	IL-4 receptor alpha	Moderate-to-severe asthma in patients $\geq$ 12 years of age with an eosinophilic phenotype or with OCS-dependent asthma (US) Severe asthma in patients aged $\geq$ 12 y with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high-dose ICS plus another medicinal product for maintenance treatment (EU)	An initial dose of 400 mg SC (two 200-mg injections) followed by 200 mg SC given every other week, OR An initial dose of 600 mg SC (two 300-mg injections) followed by 300 mg SC given every other week (US) For severe asthma patients taking OCS, the first dose is two injections of 300 mg SC in two different sites, followed by one 300-mg SC injection every 2 weeks (EU) For all other asthma patients, the first dose is two injections of 200 mg SC in two different sites, followed by one 200-mg SC injection every 2 weeks (EU)	↓ Asthma exacerbations, ↑ FEV ₁

EU, European Union; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; OCS, oral corticosteroids; IV, intravenously; q, every; QoL, quality of life; SC, subcutaneously; the US, United States; vs., versus; wk, week; wt, weight; y, years old; ↓, reduction; ↑, increase.

binds to free IgE, diminishing cell-bound IgE, downregulating IgE receptors, and preventing proinflammatory mediator release from immunocompetent cells.²⁶

Many randomized controlled trials (RCT) documented the efficacy and safety of omalizumab in children and adolescents with asthma.^{27–30} Specifically, trials found that omalizumab reduced the rate of asthma exacerbations (omalizumab vs. placebo after 52 weeks of treatment: 43% reduction [RR, 0.57 (95% CI: 0.45–0.73); $P < 0.001$]³⁰; the number of severe asthma exacerbations requiring hospitalization (omalizumab vs. placebo after 24 weeks of treatment: 44% reduction [RR, 0.55 (95% CI: 0.32–0.95); $P = 0.031$]³⁰; and the related need of OCS in children with severe asthma (median dose reduced from 20 to 5 mg/d, $P < 0.0001$).²⁸ Studies also showed omalizumab improved asthma control (median asthma control test score significantly increased from 11 to 18, $P = 0.0021$) and quality of life in patients and caregivers (omalizumab vs. placebo: 80 vs. 72%, $P < 0.001$ for comparison across all five Global Evaluation of Treatment Effectiveness categories).^{30,31} Restored antiviral defenses (in particular, type I interferon production) were recently demonstrated.^{28–31}

A series of real-world studies confirmed these positive outcomes, namely after 52 weeks of treatment, a mean 72% reduction rate in exacerbations has been reported versus baseline [1.25 (95% CI: 0.55–1.95) vs. 4.4 (95% CI: 3.7–5.2); $P < 0.0001$]. In addition, there was a significant reduction in the proportion of patients requiring hospitalization (6.7% vs. 44%, $P < 0.001$); and improvement in asthma control (good control, 67% vs. 0%).^{24,29–32} Discontinuation of daily OCS, a decrease of ICS dose (30% reduction, $P < 0.0001$), and a slight improvement in lung function [mean FEV₁ + 4.9% (95% CI: 0.69–9.19); $P = 0.023$] were also reported.^{32–35}

Safety issues have been widely studied and summarized in many RCTs showing that omalizumab is well-tolerated.^{26,31,36–40} Observational studies evidenced that local reactions (pain at the injection site and skin reactions) were the most common self-limiting adverse event (AE).^{32–35} A small risk of omalizumab-associated anaphylaxis (0.1%–0.2%) has been described in adults and adolescents receiving anti-IgE therapy, particularly in a subset of patients with a history of anaphylaxis. Anaphylaxis and drug-related serious AEs have never been reported in children 6–11 years of age.²⁷ A prospective cohort of 7,857 adolescents and adults noted no increased malignancy risk with omalizumab when compared with control [hazard ratio (HR) 1.09, 95% CI: 0.87–1.38],^{38–40} but more prolonged follow-up is needed.

As for predictive value, there is no validated biomarker able to identify responders. However, a series of parameters have been proposed as predictive factors, including >12 years of age,³² history of a recent asthma exacerbation and hospitalization in the past 6 months,³⁰ and forced expiratory volume in one second (FEV₁) <90% of predicted value.⁴¹ Severe asthma with allergic comorbidities (such as atopic dermatitis and food allergy), multiple sensitizations, eosinophilia (>300 cells/ μ L), elevated total IgE, and fractional exhaled nitric oxide (FeNO) could be significant predictors.^{42,43}

Other conditions could be favorably treated with omalizumab, such as nonallergic asthma⁴⁴ and hyper-IgE syndrome.⁴⁵ Currently, a single pediatric study is evaluating the disease-modifying effect of anti-IgE therapy in preschoolers with uncontrolled asthma (Table 2).⁴⁶ Data on optimal treatment duration and discontinuation are limited to adult studies.^{47–50}

Only one prospective real-life study reported asthma outcomes in children discontinuing omalizumab after long-term treatment: 35 children with good control and no severe exacerbation stopped omalizumab after a course of at least 24 months of treatment. Of this group, three-quarters successfully achieved discontinuation, with no clinical or lung function worsening compared with those still on omalizumab. Based on their experience, the authors suggested omalizumab discontinuation after long-term use (>2 years) in children with nonactive allergic disease, prolonged controlled asthma, and no severe exacerbations for at least 1 year.⁵¹ Further, the optimal duration of treatment and long-lasting effect should be better defined for the pediatric population.

Mepolizumab

Mepolizumab is a murine humanized immunoglobulin (IgG1 monoclonal antibody against circulating IL-5), and it has an indication of add-on maintenance therapy for severe eosinophilic asthma.^{52–54} The FDA⁵² and the EMA⁵³ approved mepolizumab as add-on treatment in patients > age 6 with severe refractory eosinophilic asthma.

Mepolizumab is administered per subcutaneous route once every 4 weeks, 100 mg for adolescents aged 12 years and over, and 40 mg for children aged 6–11 years old.^{52,53} A real-life study proposed three criteria for defining responders,⁵⁵ including patient-reported improvement of symptoms, quality-of-life (QoL), exacerbations, and physical fitness. Reduction of blood eosinophilia and OCS use,^{56,57} and improvement in FEV₁ have also been proposed.⁵⁵

There is no evidence suggesting when to discontinue mepolizumab. The National Institute for Health and Care Excellence (NICE) recommended continuing mepolizumab if there is at least a 50% reduction in exacerbation frequency at the 12th month of treatment.⁵⁸ Continued treatment is needed to maintain mepolizumab efficacy.⁵⁹ It has been reported that discontinuing treatment after 12 months entailed asthma relapse by 3–6 months, characterized by an increase in blood eosinophils, severe asthma exacerbations, and Asthma Control Questionnaire-5 (ACQ-5) score.⁶⁰

The Dose-Ranging, Efficacy, and Safety with Mepolizumab in Severe Asthma (DREAM) and the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) trials reported a significant decrease in the number of asthma exacerbations (ranging from 48% to 61% and from 47% to 53% reduction for all tested doses of mepolizumab vs. placebo, respectively) and in asthma QoL and asthma control scores ($P < 0.001$ for all comparisons).^{61,62} Moreover, the Steroid Reduction with Mepolizumab (SIRIUS) study documented a 50% median reduction in OCS use ($P = 0.007$) and a significant clinical and FEV₁ improvement.⁵⁶ The COSMOS study showed a long-lasting and stable effect of mepolizumab in reporting a low prevalence of exacerbations requiring hospitalization and emergency department visits (9% and 6%, respectively), a decrease in daily OCS dose (10.0 mg/d at baseline to 2.5 mg/d), and improvement in FEV₁ and ACQ-5 over time.⁶³ The Long-Term Extension Safety Study of Mepolizumab in Asthmatic Subjects (COLUMBA) trial reported a 56% reduction in exacerbation rates/year, ~50% of patients achieving an improvement of 0.47 points from baseline in ACQ-5 score, and a 78% reduction in blood eosinophils.⁶⁴ In all these clinical trials, the study patients were aged 12 years and older.

TABLE 2. ACTIVE AND RECRUITING CLINICAL STUDIES FOR BIOLOGICS INCLUDING PEDIATRIC POPULATION AFFECTED BY ASTHMA

<i>Study title</i>	<i>Study design and characteristics</i>	<i>Interventions & drugs</i>
Mepolizumab		
A Safety and Efficacy Study of Mepolizumab in Subjects With Severe Asthma [NCT03562195]	Phase 3 <i>n</i> = 300 Ages: 12–18 years of age Primary outcome measures: number of clinically significant exacerbations of asthma	Mepolizumab: 100 mg/4 weeks Placebo Salbutamol
Long-Term Special Drug Use Investigation of Mepolizumab [NCT 03028480]	Observational <i>n</i> = 1,000 Primary outcome measures: incidence of adverse drug reaction	Mepolizumab: 100 mg/4 weeks
Benralizumab		
PK/PD and Long-Term Safety Study of Benralizumab in Children With Severe Eosinophilic Asthma [NCT04305405]	Phase 3 <i>n</i> = 33 Ages: 6–14 years of age Primary Outcome Measures: PK and PD evaluation	Benralizumab: Dose stratified by body weight at screening
Efficacy and Safety Study of Benralizumab in Patients With Uncontrolled Asthma on Medium to High Dose Inhaled Corticosteroid Plus LABA [NCT03186209]	Phase 3 <i>n</i> = 666 Ages: 12–75 years of age Primary outcome measures: annual asthma exacerbation rate in patients with uncontrolled asthma on medium to high-dose ICS- LABA	Benralizumab: 30 mg dose Placebo
FASENRA SCEI for Long-term Use [NCT03588546]	Phase not applicable <i>n</i> = 780 Ages: child, adult, older adult Primary outcome measures: incidence of adverse drug reactions	Benralizumab: 30 mg
Dupilumab		
Assessment of the Safety and Efficacy of Dupilumab in Children With Asthma (Liberty Asthma Excursion) [NCT03560466]	Phase 3 <i>n</i> = 377 Ages: 7–12 years Primary outcome measures: treatment-emergent adverse events	Dupilumab: Doses of dupilumab will be administered every 2 weeks for 52 weeks Asthma controller therapies Asthma reliever therapies
Evaluation of Dupilumab in Children With Uncontrolled Asthma (VOYAGE) [NCT02948959]	Phase 3 <i>n</i> = 471 Ages: 6–12 years Primary outcome measures: Annualized rate of severe exacerbation events during the placebo-controlled treatment period	Dupilumab: Doses will be administered every 2 weeks Asthma controller therapies Asthma reliever therapies
Continuation of TRAVERSE-LTS12551 Evaluating Dupilumab Safety in Patients With Asthma (Long-Term Follow-Up) [NCT03620747]	Phase 3 <i>n</i> = 750 Ages: ≥12 years of age Primary outcome measures: treatment-emergent adverse events	Dupilumab: One dose administered every 2 weeks
Efficacy and Safety Study of Dupilumab in Patients With Persistent Asthma [NCT03782532]	Phase 3 <i>n</i> = 486 Ages: ≥12 years of age Primary outcome measures: change in pre-bronchodilator FEV1	Dupilumab Asthma controller therapies Asthma reliever therapies
Registry of Asthma Patients Initiating DUPIXENT (RAPID) [NCT04287621]	Observational <i>n</i> = 1,000 Ages: ≥12 years of age Primary outcome measures: baseline patient characteristics; baseline disease characteristics	Dupilumab

Adopted search strategy in clinicaltrials.gov: “asthma” as condition or disease; “omalizumab,” “mepolizumab,” and “dupilumab” as other terms; “recruiting” and/or “completed” as status; “child (birth-17)” as eligibility criteria.

FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; IL, interleukin; ILR, interleukin receptor; LABA, long-acting beta-agonist; N, number; PK, pharmacokinetics; PD, pharmacodynamics; PTS, participants; YRS, years.

This biologic has also shown a favorable safety profile, and was well tolerated.^{54,56,60,62,65} Injection-site reactions, respiratory infections, worsening of asthma, back pain, headaches, and fatigue were the most commonly reported AEs.^{54,56,62} In the clinical trials, two mepolizumab treated-subjects and zero placebo-treated subjects developed herpes zoster in studies with more than 1,300 subjects. The FDA label states that clinicians consider varicella vaccination if medically appropriate before starting therapy with mepolizumab.⁵² Subsequently, additional rare cases of herpes zoster have been reported in association with mepolizumab in adults,⁶⁶ while no such effect has been reported in children, so far.⁶⁷ No explanation for an association with herpes zoster and mepolizumab is known. Although it is a rare event, FDA recommends to consider varicella vaccination if medically appropriate before starting mepolizumab therapy.

To date, information about use of mepolizumab in children and adolescents remains limited.^{56,61–64,67}

Long-term safety, pharmacodynamic, and efficacy data from a recent study by Gupta et al. supported a positive benefit-risk profile for mepolizumab in children with severe asthma with an eosinophilic phenotype and were similar to data in studies in adults and adolescents.⁶⁸

Data from active and recruiting studies in children with asthma will add to the knowledge base (Table 2).

Reslizumab

Similar to mepolizumab, reslizumab is an IgG4 kappa monoclonal antibody, which binds specifically to IL-5 and interferes with IL-5 binding to its cell-surface receptor. This reduces the production and survival of eosinophils.

FDA approved the indication for reslizumab as an add-on maintenance therapy for adults with severe eosinophilic asthma; reslizumab has to be administered once every 4 weeks as an intravenous infusion at a recommended weight-based dose of 3 mg/kg.⁶⁹ Compared to other biologics, which are administered SC, reslizumab's IV administration may limit patient compliance.

While there is evidence of its efficacy and safety provided by some RCT conducted in adults,^{70–78} it has been reported that reslizumab was not effective in adolescents, as FEV₁ decreased, and exacerbation rates increased. Moreover, the FDA Adverse Event Reporting System (FAERS) described eosinophilic esophagitis and chronic cholecystitis in the pediatric population.⁶⁹ Evidence supporting the reslizumab use in the pediatric population is still lacking, and a dedicated clinical development plan might be desirable.

Benralizumab

Benralizumab, a murine-derived monoclonal antibody, binds the IL-5R α , and completely depletes eosinophils and modulates eosinophils-associated proteins and/or genes.⁷⁹ In 2017, this biologic was approved in the United States as add-on maintenance treatment in adolescents and adults with severe eosinophilic asthma.^{80,81} The following year, benralizumab was approved by the European Commission for add-on maintenance treatment in adults with severe eosinophilic asthma who are inadequately controlled despite treatment with high-dosage ICS and long-acting β_2 -agonists.^{80,81} Benralizumab is administered per subcutaneous route, monthly in the beginning and bi-monthly after that.⁸²

SIROCCO and CALIMA Phase III clinical trials, which enrolled adults and adolescents, showed fewer exacerbations (for all tested dose regimens $P < 0.0001$), and improved FEV₁ and symptom severity.^{83–86} Better outcomes were observed in the bimonthly schedule⁸⁷ and with higher eosinophilia at baseline.⁸⁸ However, the BISE study, another Phase III trial, did not confirm these results.⁸⁸ The BORA study retrospectively investigated the safety issue over 108 weeks of treatment in adolescents.⁸⁹ Asthma worsening was the most common AE. At present, there are no data about a possible risk of malignancies during benralizumab treatment.^{84–86,89} The clinical development program of benralizumab in the pediatric population is reported in Table 2.

Dupilumab

Dupilumab is a fully human IgG4 monoclonal antibody that blocks the shared receptor component of IL-4 and IL-13, thereby inhibiting these key drivers of type 2 inflammation.⁹⁰ It was the first biologic approved in adults and adolescents for use against moderate-to-severe atopic dermatitis (AD). Also, it was subsequently approved in the United States (2018) and in Europe (2019) as add-on maintenance treatment in adults and adolescents ≥ 12 years of age with severe asthma with an eosinophilic phenotype.⁹¹ According to the EMA, dupilumab is recommended for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or FeNO inadequately controlled with high-dose ICS plus another maintenance treatment.⁹² The FDA approved dupilumab not only for an eosinophilic phenotype, but also for OCS-dependent asthma.⁹³ In addition to these indications, dupilumab has been licensed as add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP).^{92,93} With evidence of type 2 inflammation observed across these various diseases, dupilumab is currently the best candidate among the marketed biological therapies to treat patients with multiple allergic comorbidities.

Dupilumab is available as prefilled syringes containing dupilumab 200 mg or 300 mg in a solution for subcutaneous administration at different dosages depending on age and weight (400 mg loading dose followed by 200 mg every 2 weeks in adolescents aged ≥ 12 to < 18 years with a baseline body weight of < 60 kg, or 600 mg loading dose followed by 300 mg every 2 weeks for adolescents with a baseline body weight ≥ 60 kg).^{92,93} Also, dupilumab may be safely administered at home after training in subcutaneous injection technique by a health care provider. As at-home administration is a safe, cost-effective pathway that some patients prefer, this drug is particularly appealing for the pediatric population.

Expanding the use of dupilumab to the adolescents derived from the results of the adult clinical development program. The QUEST trial enrolled 1,902 patients (≥ 12 years of age) with uncontrolled, moderate-to-severe asthma despite daily ICS therapy.⁹⁴ Dupilumab significantly reduced the annualized rate of severe asthma exacerbations (0.27 for the dupilumab group vs. 0.6 in the placebo group), mainly when eosinophilia and FeNO were very high at baseline (≥ 25 parts per billion [ppb]). The VENTURE trial showed a 70.1% reduction of OCS use in the dupilumab group, when compared with a 41.9% reduction in the placebo group ($P < 0.001$), and improvement in FEV₁ equaling 0.22 L (95% CI: 0.09–0.34) higher in the dupilumab group versus placebo.⁹⁵

The most common AEs (incidence $\geq 1\%$) in patients with asthma are injection site reactions, oropharyngeal pain, and eosinophilia. An increase of blood eosinophils was reported in both trials: only in the QUEST trial, the eosinophil count increase was associated with symptoms in 4 patients who received dupilumab, and two of these events were associated with symptoms.^{94–96} While conjunctivitis is a well-recognized AE of dupilumab AD trials, it was not observed in asthma trials and was reported in $<5\%$ of patients involved in CRSwNP trials.⁹⁷

At the time of this writing, the VOYAGE trial, which has enrolled children with asthma between 6 and 12 years of age, is still ongoing.⁹⁸ The clinical development program of dupilumab in the pediatric population with asthma is underway, and the results are highly anticipated (Table 2).

Concluding Remarks

Targeted biologic therapies have emerged as effective add-on options in children and adolescents with severe asthma. Available biologic therapies include omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. Their primary benefit has been a decrease in the frequency of asthma exacerbations, including emergency room visits, hospitalizations, and need for oral steroids. Other benefits include reduced asthma symptoms, reduced dosage of other controller medication, and less missed school and work days. Although very attractive, the use of biologics in the pediatric and adolescent age groups has some open concerns, such as safety, cost, and unclear length of treatment.

While a large body of literature regarding the safety of biologic therapies in children exists for omalizumab, few data are available for the other biologics. Of note, only 154 and 138 children between 12 and 18 years of age were enrolled in Phase III clinical trials of mepolizumab and dupilumab, respectively.⁹⁹ Furthermore, long-term safety data are available only for patients $\geq$ age 12 with moderate-to-severe allergic asthma who were treated with omalizumab. Thus, further studies are needed to address the long-term safety profile of novel biologics in the pediatric population.

In this context, two recent systematic reviews by Agache et al. determined that the observed overall effects are relatively modest, such as reducing exacerbations, while probably improving asthma control, quality-of-life, or lung function.^{100,101} These analyses of various studies led to recommendations that use of biologics should be reserved for carefully selected patients in the current environment of rising health care costs. Thus, adequate selection of patients is essential before prescribing biologics.

Practical indications for the selection of biologics in children with severe asthma are lacking or are borrowed from adults and based only on expert opinions. In pediatric practice, the presence of allergic asthma and total IgE within the omalizumab range can direct the choice of biologic initially toward omalizumab. Mepolizumab may represent the first choice in the presence of high blood eosinophils or in cases outside the IgE range or in cases of nonallergic asthma. It can also be an alternative in cases of nontherapeutic response to omalizumab.

It should be noted that the presence of biomarkers of atopy, eosinophilic and type 2 inflammation may overlap in children with asthma. The recent approval of dupilumab for pediatric severe asthma could bring the pathway of care into

question, possibly making it the first choice in patients with multiple type 2 inflammatory comorbidities. Thus, further head-to-head comparison studies of biologics are required in the pediatric population to identify new and optimal biomarkers for response to treatment to each biologic.

In conclusion, additional clinical trials conducted in children and adolescents are needed to reinforce the strength of available efficacy and safety data of biologic therapies. Moreover, their efficacy may be more pronounced in young children since there is less destruction of the bronchi and bronchiole, and allergy is probably more pronounced in adults with asthma. With these additional findings, the positioning of biologics could be more effectively implemented in the future. A thorough phenotyping and endotyping, using reliable biomarkers and considering the possible presence of asthma comorbidities, could better enable a personalized approach to therapy, tailored to each patient.

Authors' Contribution

All authors contributed to the study and the writing of the article. All authors reviewed the article. All authors have read and agreed to the published version of the article.

Author Disclosure Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding Information

No funding was received for this article.

References

1. Ramratnam SK, Bacharier LB, Guilbert TW. Severe Asthma in Children. *J Allergy Clin Immunol Pract* 2017; 5:889–898.
2. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation, and treatment of severe asthma. *Eur Respir J* 2014; 43:343–373.
3. Papi A, Brightling C, Pedersen SE, et al. Asthma. *Lancet* 2018; 391:783–800.
4. Corren J, Yawn BP. Advancing the care of severe asthma: differential diagnosis, multidisciplinary management, and patient engagement. *Am J Med* 2020 [Epub ahead of print]; DOI: 10.1016/j.amjmed.2019.02.002.
5. Ciprandi G, Tosca MA, Silvestri M, et al. Inflammatory biomarkers for asthma endotyping and personalized therapy. *Exp Rev Clin Immunol* 2017; 13:715–721.
6. Akar-Ghibril N, Casale T, Custovic A, et al. Allergic Endotypes and Phenotypes of Asthma. *J Allergy Clin Immunol Pract* 2020; 8:429–440.
7. Licari A, Ciprandi R, Marseglia GL, et al. Anxiety and depression in adolescents with severe asthma and their parents: preliminary results after 1-year treatment. *Behav Sci* 2019; 9:78.
8. Licari A, Brambilla I, Marseglia A, et al. Difficult vs. Severe Asthma: definition and Limits of Asthma Control in the Pediatric Population. *Front Pediatr* 2018; 6:170.
9. Chipps BE, Parikh NG, Maharaj SK. Severe Asthma in Children. *Curr Allergy Asthma Rep* 2017; 17:21.
10. Ferrante G, La Grutta S. The Burden of Pediatric Asthma. *Front Pediatr* 2018; 6:186.

11. Fitzpatrick AM. Severe asthma in children: lessons learned and future directions. *J Allergy Clin Immunol Pract* 2016; 4:11–19.
12. Fleming L, Murray C, Bansal AT, et al. The burden of severe asthma in childhood and adolescence: results from the pediatric U-BIOPRED cohorts. *Eur Respir J* 2015; 46: 1322–1333.
13. Montella S, Baraldi E, Cazzato S, et al. Severe asthma features in children: a case-control online survey. *Ital J Pediatr* 2016; 42:9.
14. Licari A, Castagnoli R, Brambilla I, et al. Asthma endotyping and biomarkers in childhood asthma. *Pediatr Allergy Immunol Pulmonol* 2018; 31:44–55.
15. Robinson D, Humbert M, Buhl R, et al. Revisiting type 2-high and Type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy* 2017; 47:161–175.
16. Samitas K, Zervas E, Gaga M. T2-low asthma: current approach to diagnosis and therapy. *Curr Opin Pulm Med* 2017; 23:48–55.
17. Manti S, Brown P, Perez MK, et al. The role of neurotrophins in inflammation and allergy. *Vitam Horm* 2017; 104:313–341.
18. Ricciardolo F, Sorbello V, Folino A, et al. Identification of IL-17F/frequent exacerbator endotype in asthma. *J Allergy Clin Immunol* 2017; 140:395–406.
19. Ciprandi G, Cuppari C, Salpietro AM, et al. Serum IL-23 strongly and inversely correlates with FEV1 in asthmatic children. *Int Arch Allergy Immunol* 2012; 159:183–186.
20. Licari A, Castagnoli R, Brambilla I, et al. New approaches for identifying and testing potential new anti-asthma agents. *Expert Opin Drug Discov* 2018; 13:51–63.
21. Licari A, Marseglia GL. Current and future challenges in severe pediatric asthma. *Curr Med Res Opin* 2018; 34:943–944.
22. Ciprandi G, Marseglia GL, Castagnoli R, et al. From IgE to clinical trials of allergic rhinitis. *Expert Rev Clin Immunol* 2015; 11:1321–1333.
23. Licari A, Marseglia G, Castagnoli R, et al. The discovery and development of omalizumab for the treatment of asthma. *Expert Opin Drug Discov* 2015; 10:1033–1042.
24. Xolair. FDA Highlights of prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf Accessed July 18, 2020.
25. Xolair. EMA Summary of Product Characteristics. Available at: www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-xolair-25-june-2009_en.pdf Accessed July 18, 2020.
26. Licari A, Marseglia A, Caimmi S, et al. Omalizumab in children. *Paediatr Drugs* 2014; 16:491–502.
27. Chipps BE, Lanier B, Milgrom H, et al. Omalizumab in children with uncontrolled allergic asthma: review of clinical trial and real-world experience. *J Allergy Clin Immunol* 2017; 139:1431–1444.
28. Brodli M, McKean MC, Moss S, et al. The oral corticosteroid-sparing effect of omalizumab in children with severe asthma. *Arch Dis Child* 2012; 97:604–609.
29. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364:1005–1015.
30. Lanier B, Bridges T, Kulus M, et al. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009; 124:1210–1216.
31. Teach SJ, Gill MA, Togias A, et al. Pre seasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015; 136:1476–1485.
32. Rodrigo GJ, Neffen H. Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents. *Pediatr Allergy Immunol* 2015; 26:551–556.
33. Deschildre A, Marguet C, Salleron J, et al. Add-on omalizumab in children with severe allergic asthma: a 1-year real-life survey. *Eur Respir J* 2013; 42:1224–1233.
34. Deschildre A, Marguet C, Langlois C, et al. Real-life long-term omalizumab therapy in children with severe allergic asthma. *Eur Respir J* 2015; 46:856–859.
35. Licari A, Castagnoli R, Denicolò C, et al. Omalizumab in Children with Severe Allergic Asthma: The Italian Real-Life Experience. *Curr Respir Med Rev* 2017; 13:36–42.
36. Pitrez PM, de Souza RG, Roncada C, et al. Impact of omalizumab in children from a middle-income country with severe therapy-resistant asthma: a real-life study. *Pediatr Pulmonol* 2017; 52:1408–1413.
37. Berger W, Gupta N, McAlary M, et al. Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol* 2003; 91:182–188.
38. Milgrom H, Fowler-Taylor A, Vidaurre CF, et al. Safety and tolerability of omalizumab in children with allergic (IgE-mediated) asthma. *Curr Med Res Opin* 2011; 27: 163–169.
39. Busse W, Buhl R, Fernandez Vidaurre C, et al. Omalizumab and the risk of malignancy: results from a pooled analysis. *J Allergy Clin Immunol* 2012; 129:983–989.e6.
40. Long A, Rahmaoui A, Rothman KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol* 2014; 134:560–567.e4.
41. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014; 1:CD003559.
42. Busse W, Haselkorn T, Rosén K, et al. Greater Treatment Benefit with Omalizumab in Children with Increased Asthma Severity: Exploratory Analyses from the Inner-City Anti-IgE Therapy for Asthma (ICATA) Study. *J Allergy Clin Immunol* 2018; 141(2 Suppl):AB14.
43. Sesé L, Schneider M, Bourgoin M, et al. Asthma with multiple allergic comorbidities is associated with complete response to omalizumab. *Clin Exp Allergy* 2019; 49: 733–735.
44. Bourgoin-Heck M, Amat F, Trouvé C, et al. omalizumab could be effective in children with severe eosinophilic non-allergic asthma. *Pediatr Allergy Immunol* 2018; 29:90–93.
45. Wang KY, Sindher SB, Stinson R, et al. Efficacy and safety of omalizumab in pediatric patients with high immunoglobulin E levels: a case series. *Allergy Asthma Proc* 2018; 39:289–291.
46. Preventing Asthma in High Risk Kids (PARK). ClinicalTrials.gov Identifier: NCT02570984. Available at: <https://clinicaltrials.gov/ct2/show/NCT02570984> Accessed July 18, 2020.
47. Nopp A, Johansson SGO, Adédoyin J, et al. After 6 years with Xolair; a 3-year withdrawal follow-up. *Allergy* 2010; 65:56–60.
48. Molimard M, Mala L, Bourdeix I, et al. Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control. *Respir Med* 2014; 108:571–6.

49. Vennera MDC, Sabadell C, Picado C, et al. Duration of the efficacy of omalizumab after treatment discontinuation in 'real life' severe asthma. *Thorax* 2017; 73:782–4.
50. Ledford D, Busse W, Trzaskoma B, et al. A Randomized, Multicenter Study Evaluating Xolair® Persistency Of Response After Long-Term Therapy (XPORT). *J Allergy Clin Immunol* 2017; 140:162–9.
51. Deschildre A, Roussel J, Drumez E, et al. Omalizumab discontinuation in children with severe allergic asthma: an observational real-life study. *Allergy* 2019; 74:999–1003.
52. Nucala prescribing information. Available at: www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF Accessed July 18, 2020.
53. Nucala EMA product information. Available at: www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf Accessed July 18, 2020.
54. Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate the safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007; 176:1062–1071.
55. Drick N, Seeliger B, Welte T, et al. Anti-IL-5 therapy in patients with severe eosinophilic asthma - clinical efficacy and possible criteria for treatment response. *BMC Pulm Med* 2018; 18:119.
56. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371:1189–1197.
57. Halder P. Patient profiles and clinical utility of mepolizumab in severe eosinophilic asthma. *Biologics* 2017; 11: 81–95.
58. Mepolizumab for treating severe refractory eosinophilic asthma_NICE. Available at: www.nice.org.uk/guidance/ta431 Accessed September 24, 2020.
59. Halder P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. *J Allergy Clin Immunol* 2014; 133:921–923.
60. Farne HA, Wilson A, Powell C, et al. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev* 2017; 9:CD010834.
61. Pavord ID, Kom S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380:651–659.
62. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371:1198–1207. Erratum in: *N Engl J Med* 2015; 372:1777.
63. Lugogo N, Domingo C, Chanez P, et al. Long-term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-center, Open-label, Phase IIIb Study. *Clin Ther* 2016; 38:2058–2070.e1.
64. Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol* 2019; 143:1742–1751.e7.
65. Henriksen DP, Bodtger U, Sidenius K, et al. Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti-IL-5 treatments of severe asthma - a systematic review and meta-analysis. *Eur Clin Respir J* 2018; 5:1536097.
66. Rosati B, Bochner BS, Peters AT. Mepolizumab for treatment of asthma: post-approval academic practice experience. *J Allergy Clin Immunol* 2018; 141:AB11.
67. Gupta A, Steinfeld J, Price RG, et al. Mepolizumab for severe eosinophilic asthma: a comparison of efficacy in children, adolescents, and adults. Poster No: PA5447. ERS 2018. *Eur Respir J* 2018; 52.
68. Gupta A, Ikeda M, Geng B, et al. Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. *J Allergy Clin Immunol* 2019; 144:1336–1342.e7.
69. Logan JK, Harinstein L, Muñoz M. Pediatric Postmarketing Pharmacovigilance Review: Cinqair (Reslizumab). Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM610723.pdf Accessed July 18, 2020.
70. Corren J, Weinstein S, Janka L, et al. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest* 2016; 150: 799–810.
71. Bjermer L, Lemiere C, Maspero J, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest* 2016; 150:789–798.
72. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts results from two multicentre, parallel, double-blind, randomized, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3:355–366.
73. Brusselle G, Germinaro M, Weiss S, et al. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. *Pulm Pharmacol Ther* 2017; 43:39–45.
74. Chanez P, McDonald M, Garin M, et al. Early decreases in blood eosinophil levels with reslizumab. *J Allergy Clin Immunol* 2019; 143:1653–1655.
75. Murphy K, Jacobs J, Bjermer L, et al. Long-term Safety and Efficacy of Reslizumab in Patients with Eosinophilic Asthma. *J Allergy Clin Immunol Pract* 2017; 5:1572–1581.e3.
76. Mukherjee M, Aleman Paramo F, Kjarsgaard M, et al. Weight-adjusted Intravenous Reslizumab in Severe Asthma with Inadequate Response to Fixed-Dose Subcutaneous Mepolizumab. *Am J Respir Crit Care Med* 2018; 197:38–46.
77. Bateman ED, Djukanović R, Castro M, et al. Predicting responders to reslizumab after 16 weeks of treatment using an algorithm derived from clinical studies of severe eosinophilic asthma patients. *Am J Respir Crit Care Med* 2019; 199:489–495.
78. Sridhar S, Liu H, Pham TH, et al. Modulation of blood inflammatory markers by benralizumab in patients with eosinophilic airway diseases. *Respir Res* 2019; 20:14.
79. Fasenra. FDA highlights of prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf Accessed July 18, 2020.
80. AstraZeneca. Fasenra (benralizumab). Summary of product characteristics. 2018. Available at: http://ec.europa.eu/health/documents/communityregister/2018/20180108139598/anx_139598_en.pdf Accessed July 18, 2020.
81. Matera MG, Calzetta L, Rinaldi B, et al. Pharmacokinetic/pharmacodynamic drug evaluation of benralizumab for the treatment of asthma. *Expert Opin Drug Metab Toxicol* 2017; 13:1007–1013.
82. Bagnasco D, Caminati M, Ferrando M, et al. Anti-IL-5 and IL-5Ra: efficacy and safety of new therapeutic strategies in severe uncontrolled asthma. *Biomed Res Int* 2018; 5698212.
83. Bleecker ER, Wechsler ME, Fitzgerald JM, et al. Baseline patient factors impact on the clinical efficacy of benrali-

- zumab for severe asthma. *Eur Respir J* 2018; 52. pii: 1800936.
84. Bleecker ER, Fitzgerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting $\beta(2)$ -agonists (SIROCCO): a randomized, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388:2115–2127.
 85. Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as an add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2128–2141.
 86. Nair P, Wenzel S, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med* 2017; 376:2448–2458.
 87. Chia YL, Yan L, Yu B, et al. Relationship between benralizumab exposure and efficacy for patients with severe eosinophilic asthma. *Clin Pharmacol Ther* 2019; 106:383–390.
 88. Ferguson GT, Fitzgerald JM, Bleecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2017; 5: 568–576.
 89. Busse WW, Bleecker ER, Fitzgerald JM, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med* 2019; 7:46–59.
 90. Santini G, Mores N, Malerba M, et al. Dupilumab for the treatment of asthma. *Expert Opin Invest Drugs* 2017; 26: 357–366.
 91. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting $\beta(2)$ agonist: a randomized, double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016; 388:31–44.
 92. Dupixent. EMA Summary of Product Characteristics. Available at: www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf Accessed July 18, 2020.
 93. Dupixent. FDA highlights of prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2018/761055s0071b1.pdf Accessed July 18, 2020.
 94. Sanofi Evaluation of dupilumab in patients with persistent asthma (Liberty asthma quest). Available at: <https://clinicaltrials.gov/ct2/show/NCT02414854>. NLM identifier: NCT02414854. Accessed September 20, 2020.
 95. Sanofi Evaluation of dupilumab in patients with severe steroid-dependent asthma (VENTURE). Available at: <https://clinicaltrials.gov/ct2/show/NCT02528214>. NLM identifier: NCT02528214. Accessed September 20, 2020.
 96. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018; 378:2475–2485.
 97. Licari A, Castagnoli R, Marseglia A, et al. Dupilumab to treat type 2 inflammation in children and adolescents. *Ped Drugs* 2020; 22:295–310.
 98. Sanofi Evaluation of dupilumab in children with uncontrolled asthma (VOYAGE). Available at: <https://clinicaltrials.gov/ct2/show/NCT02948959>. NLM identifier: NCT02948959. Accessed September 20, 2020.
 99. Lovinsky-Desir S. The use of biologic therapies for the management of pediatric asthma. *Pediatr Pulmonol* 2020; 55:803–808.
 100. Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe eosinophilic asthma. *Allergy* 2020; 75:1023–1042.
 101. Agache I, Rocha C, Beltran J, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, and omalizumab) for severe allergic asthma. *Allergy* 2020; 75: 1043–1057.

Address correspondence to:

Giorgio Ciprandi, MD

Allergy Clinic

Casa di Cura Villa Montallegro

Via P. Boselli 5,

Genoa 16146

Italy

E-mail: gio.cip@libero.it

Received for publication May 17, 2020; accepted after revision October 4, 2020.