Biologics: Targets and Therapy

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REVIEW

Biological Therapies in Children and Adolescents with Severe Uncontrolled Asthma: A Practical Review

Martina Votto[1,2,*]
Maria De Filippo[1,2,*]
Amelia Licari[1,2]
Alessia Marseglia[2]
Mara De Amici[3]
Gian Luigi Marseglia[1,2]

[1]Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; [3]Immuno-Allergology Laboratory, Clinical Chemistry Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

*These authors contributed equally to this work

Abstract: Severe uncontrolled asthma is a complex and heterogeneous disease. A multidisciplinary assessment is required to correctly identify and manage children and adolescents with severe asthma because they may require strict monitoring and additional treatment with advanced targeted therapies. Recent research efforts have focused on identifying epidemiologic, clinical, and molecular mechanisms that underlie severe asthma, leading to the recognition of different phenotypes and endotypes and identifying biomarkers able to predict the response to biologic therapies. Additional progress has occurred by introducing biological therapies that have revolutionized the care of chronic allergic diseases in the adult and pediatric population. In this review, we briefly summarized the current literature on biological therapies to treat severe asthma in children and adolescents.

Keywords: severe asthma, children, adolescents, biological therapy, endotype, phenotype

Introduction

Atopic diseases are multifactorial disorders resulting from the interactions of genetic predisposition, impaired immune response, environmental and lifestyle risk factors, influencing disease onset, clinical expressivity, and variability of illness severity.[1,2] Allergic diseases showed a remarkably increased prevalence in the last decades.[1,2] The global health burden of severe allergic diseases is relevant since patients may experience disability, anxiety and emotional distress, social restrictions, and reduced quality of life (QoL).[3–6] Despite some progress made in understanding the pathogenesis of atopic diseases, significant differences in clinical characteristics, treatment response, and natural history have been described in many allergic patients treated with conventional therapies. To date, studies that aim to identify potential cellular and molecular signature (endotypes) have given rise to new targeted and specific treatment strategies for precision medicine and individualized therapies in allergic disorders.[7,8]

In this brief review, we summarize current evidence on available biological therapies to treat severe asthma phenotypes in children and adolescents.

Severe Asthma in Pediatrics

Severe asthma is a chronic airway disease characterized by respiratory symptoms that affects about 0.23–0.5% of children and adolescents.[9] Pediatric patients with severe uncontrolled asthma generally show a reduced QoL due to troublesome persistent

Correspondence: Amelia Licari
Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, p.le C. Golgi n.19, Pavia, 27100, Italy
Tel/Fax +390382502629
Email amelia.licari@unipv.it

Received: 2 March 2021
Accepted: 19 April 2021
Published: 5 May 2021

respiratory symptoms, neuropsychological issues, missed school days, recurrent life-threatening asthma attacks, and side effects of systemic corticosteroids.[10,11] According to current guidelines, severe asthma is defined by persistent/recurrent asthmatic symptoms or acute asthma attacks despite high doses of inhaled and/or oral corticosteroids (OCS) (Table 1).[12–14] Diagnosis of severe uncontrolled asthma requires a multidisciplinary assessment and the exclusion of asthma-mimicking conditions (Table 2).[15] After evaluating comorbidities (sinus disease, gastroesophageal reflux, obesity, anxiety, and depression) and modifiable treatment-related issues (non-adherence to medication, improper inhalation technique, persistent adverse environmental exposures, and emotional factors), additional biologic therapies may be prescribed in children and adolescents with uncontrolled asthma.[16–18]

Severe pediatric asthma is a highly heterogeneous disease with multiple phenotypes.[9,11] Several research efforts have been addressed to identify clinical phenotypes of severe pediatric asthma in the last years. Compared to adult-onset, early-onset asthma is usually characterized by high levels of total serum immunoglobulin E (IgE), blood eosinophilia, and aeroallergen polysensitization. However, a small group of pediatric patients showed a reduction in their lung function and small airway hyperresponsiveness.[19–21] Several studies on cluster analyses have been realized to classify children with severe asthma into subgroups with shared clinical features.[22] Childhood severe asthma subgroups are mainly represented by sex, multiple allergic sensitization and comorbidities, degree of airway obstruction, rates of exacerbation, age of asthma onset (> 15 years), body mass index, the dose of OCS, and nasal symptoms.[22]

The clinical classification of asthma cannot predict the response to advanced therapies, such as biologics. Therefore, current research shifted from the phenotype evaluation towards identifying cellular and molecular mechanisms (endotypes) and related biomarkers of severe asthma that could predict the response to therapies and assist in designing personalized therapies.[8,23]

Table 2 Differential Diagnosis of Severe Uncontrolled Asthma

Toddlers	Children and Adolescents
Tracheobronchomalacia Bronchopulmonary Dysplasia Tuberculosis Cystic Fibrosis Primary Ciliary Dyskinesia Obliterative bronchiolitis Immunodeficiencies Foreign body Vascular rings	Vocal cord dysfunction Hyperventilation Exercise-induced hyperventilation

Table 1 Definitions of Severe Uncontrolled Asthma

Guidelines	Definitions	High Dose Therapy	Poor Control	Exacerbations
European Respiratory Society/American Thoracic Society (ERS/ATS) 2020[12]	Asthma that requires treatment with high dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy.	Yes	Yes	No
Global Initiative for the treatment of Asthma (GINA) 2020[13]	Asthma that requires GINA Step 4 or 5 treatment or such treatment to maintain good symptom control and reduce exacerbations (≥2/year or ≥1/year requiring hospitalization). Asthma is uncontrolled despite adherence with maximal optimized Step 4 or Step 5 therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased.	Yes	Yes	Yes
British Thorac Society (BTS) 2016[14]	A prior diagnosis of asthma exists, and asthma-like symptoms and asthma attacks persist, despite prescription of high-dose asthma therapy (medium-dose ICS plus a LABA or LTRA; low-dose ICS plus a LABA or LTRA and an appropriate additional therapy; or continuous or frequent use of oral steroids).	Yes	Yes	Yes

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LTRA, leukotriene receptor antagonists.

To date, two main endotypes of severe asthma have been proposed based on the type of airway inflammation: type 2 (T2)-high and T2-low asthma endotypes.[8] The pathogenetic mechanisms of the T2-high endotype are driven by IgE and specific cytokines. Innate and adaptive immune cells release interleukin (IL)-4, IL-5, and IL-13 that are the pivotal mediators of type 2 inflammation.[24] The T2-high endotype is the most common in childhood, and clinically matches with the early onset asthma phenotype; in fact, this endotype generally shows an airway eosinophilic inflammation and multiple allergic sensitizations. On the other hand, the neutrophilic or paucigranulocytic airway inflammation characterizes the T2-low asthma endotype, which is less common in childhood.[25,26] In particular, the T2-low inflammation is mainly sustained by IL-8, IL-17, IL-22, other T cell-related cytokines, and epithelial cell-derived cytokine.[25,26]

In the last years, more complete asthma pathogenesis efforts have allowed the emergence and the clinical application of new biological therapies, mainly targeting type 2 inflammation.[27,28]

Omalizumab

Mechanism of Action and Dosage

The pharmacological blockade of IgE was the first successful strategy for severe asthma. Thus, omalizumab was the first humanized monoclonal anti-IgE with a pediatric indication (Table 3).[29,30] By binding to circulating IgE, omalizumab directly prevents their interaction with the IgE receptor (FCεR1) on the mast cells and basophil surface, inhibiting the release of pro-inflammatory mediators.[31] Besides, omalizumab indirectly downregulates the expression of FCεR1.[31]

Omalizumab is recommended as an additional therapy for children (age ≥ six years) with allergic asthma showing elevated serum IgEs (> 30 and < 1500 IU/mL) and positive sensitization to one or more perennial aeroallergens.[15] The

Table 3 Sum of Biological Therapies for Severe Asthma Management in Pediatrics

Biological Therapy	Mechanism of Action	Indication	Population	Dosage	Criteria of Response to Therapy	Common Side Effects
Omalizumab	Anti-IgE	Add-on treatment of severe allergic asthma with elevated IgE and positive specific IgE at least one aeroallergen.	Children ≥ 6 years, adolescents and adults	SC injection every 2 or 4 weeks. Dose and frequency of dosing are guided by a nomogram.	Serum IgE > 30 < 1500 IU/mL Perennial aeroallergen Blood eosinophil count ≥ 300 cells/μL	Local skin reaction and pain, anaphylaxis (0.1–0.2% of adults and adolescents).
Mepolizumab	Anti-IL-5	Add on therapy in patients with severe asthma with an eosinophilic phenotype, and a history of asthma exacerbations.	Adults and children ≥ 6 years	100 mg SC every 4 weeks in adults and adolescents ≥ 12 years. 40 mg SC every 4 weeks in children aged 6–11 years.	Blood eosinophil count ≥ 300 cells/μL, or blood eosinophil count ≥ 150 cells/μL in patients with well characterized eosinophilic asthma or requiring regular OCS.	Infections, worsening of asthma, headache, local skin reactions, back pain, fatigue.
Dupilumab	Anti-IL-4 receptor α-subunit, blocking signaling induced by both IL-4 and IL-13.	Add-on treatment of severe asthma with type 2 inflammation, peripheral eosinophilia and high values of FeNo.	Adults and adolescents ≥ 12 years	1)For severe asthma in patients taking OCS or in patients with AD and CRSwNP first dose is 2 injections of 300 mg followed by 300 mg every 2 weeks. 2)For all other patients with asthma the first dose is 2 injections of 200 mg followed by one injection of 200 mg.	Peripheral eosinophilia (≥ 150 cells/μL), and/or FeNo ≥ 25 ppb	Injection-site erythema, pain, edema, pruritus, conjunctivitis, eye pruritus, blepharitis, oral herpes, eosinophilia, headache.

Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; FeNo, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin, OCS, oral corticosteroid; SC, subcutaneous.

dose and frequency of subcutaneous (SC) administrations of omalizumab are established by a nomogram obtained from total serum IgE levels and body weight (kilograms).[30] Recent studies demonstrated that omalizumab is more effective in asthmatic children showing multiple allergic comorbidities (multiple sensitizations, atopic dermatitis, and food allergy), and high peripheral eosinophil counts (> 300 cells/μL), pretreatment total IgE, fractional exhaled nitric oxide (FeNO > 20 ppb) and elevated serum periostin.[32,33] Nevertheless, there are not enough data on validated biomarkers predicting response to omalizumab therapy in children; thus, further investigation is needed.[28,34]

Efficacy and Safety

Several randomized controlled trials established the efficacy and safety of omalizumab in pediatrics.[35–38] Notably, pediatric studies reported that omalizumab reduced the rate of acute asthma attacks, hospitalizations, and the need for OCS.[39–43]

Besides, omalizumab significantly improved the asthma control and the QoL of patients.[39–43] Finally, pediatric patients treated with omalizumab developed a lower number of seasonal exacerbations induced by respiratory viruses than controls.[35–37]

A large amount of data from trials and prospective studies showed that omalizumab is generally well tolerated in children and adolescents.[31,39,44–48] The risk of severe or life threatening drug-related events, such as anaphylaxis, has been reported in 0.1–0.2% of adults and adolescents treated with omalizumab and was not observed in pediatric studies.[44–46] Local skin reaction and pain at the injection site are the main side effects reported in observational studies and generally have a quick resolution.[40–42] Finally, there is no evidence to support an increased risk of malignancy. However, long-term monitoring studies on patients treated with omalizumab are still needed to confirm the good safety profile.[28,34,46,47]

Mepolizumab

Mechanism of Action and Dosage

Mepolizumab is a humanized monoclonal antibody that binds to and inhibits circulating IL-5. Mepolizumab has recently been approved as additional maintenance therapy for severe eosinophilic asthma (Table 3).[49,50] The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recently approved the use of mepolizumab in asthmatic patients aged ≥ 6 years with refractory disease, an eosinophilic phenotype, and a history of asthma exacerbations.[51,52]

Currently, the recommended dosage of mepolizumab is 100 mg for adults and children aged ≥ 12 years, and 40 mg for children aged 6–11 years.[53]

Although standardized response criteria are still lacking, clinical and laboratory parameters have been proposed as predictor tools for therapy response.[54] Blood eosinophil count ≥ 300 cells/μL, (or ≥ 150 cells/μL in patients with well-characterized eosinophilic asthma or requiring several cycles with OCS) and, more recently, the improvement in FEV1 value are currently considered as parameters of response to mepolizumab therapy.[54–56] Moreover, the improvement of QoL, exacerbations, and physical fitness have also been reported as clinical predictors for response to therapy.[56]

There is no validated recommendation on mepolizumab discontinuation. According to the National Institute for Health and Care Excellence (NICE) guidelines, the decision to continue mepolizumab therapy is based on more than 50% of reduction of asthma exacerbations after 12 months of treatment.[57] Besides, as reported in several studies, continued dosing is required to maintain the positive therapeutical effect.[54] It was reported that patients who discontinued mepolizumab might relapse after 3–6 months, showing high peripheral eosinophilia, and a significant increase in asthma attack rate, and the Asthma Control Questionnaire-5 (ACQ-5) score.[58]

Efficacy and Safety

Two double-blind, randomized, placebo-controlled trials evaluated the efficacy and safety of mepolizumab in adults and adolescents with uncontrolled eosinophilic asthma.[59,60] Moreover, these trials showed a significant decrease in the rate of asthma exacerbations and QoL, mostly in patients with a baseline blood eosinophil count of at least 500 cells/μL.[59] In a recent trial, Khatri et al evaluated the long-term efficacy of mepolizumab. Although only a small proportion of adolescents were enrolled in this study, all pediatric patients had reached the endpoints, including the annualized severe exacerbation rates, changes from baseline in ACQ-5 score, and blood eosinophil counts.[61] The Steroid Reduction with Mepolizumab (SIRIUS) study showed that patients treated with mepolizumab reported a significant reduction in OCS use and a remarkable improvement in their symptoms and lung function.[55] Besides, the COSMOS study highlighted a long-lasting and stable effect in the mepolizumab group over time and a significant improvement of FEV1 and ACQ-

5 score.[62] There is poor evidence of the effectiveness of mepolizumab in asthmatic children younger than 12 years. In the open-label study by Gupta et al the primary endpoint was the assessment of the pharmacokinetics and pharmacodynamics in children with 6 to 11 years-of-age; thus, the efficacy of mepolizumab was difficult to evaluate.Therefore further research is needed.[63]

In placebo-controlled trials, mepolizumab also showed a notable safety profile and appeared well tolerated.[50,55,58,60,63] The most commonly reported side effects were reactions at the site of injection, headaches, fatigue, respiratory infections, and worsening of asthma.[50,55,60,64]

Reslizumab

Mechanism of Action and Dosage

Reslizumab is a monoclonal antibody that binds circulating IL-5. Reslizumab was approved as additional therapy for patients with severe uncontrolled eosinophilic asthma aged ≥ 18 years.[65] In particular, the NICE Appraisal Committee recommends the use of reslizumab for the treatment of severe asthma despite a high-dose ICS plus another therapy, when: 1) peripheral eosinophils are ≥ 400 cells/μL, 2) patient had ≥ three asthma exacerbations in a year, and 3) company provides the monoclonal antibody at the agreed discount level.[66] The recommended dosage of reslizumab is 3.0 mg/kg IV every 4 weeks.[67]

Bateman et al proposed as responder criteria 1) an improvement of the ACQ and Assessment of Quality of Life (AQoL), 2) pretreatment value of FEV1 and 3) the number of asthma attacks during the year before the beginning of therapy and the first 16 weeks of treatment.[68] However, these parameters are not validated, and further studies are required.[68] Data on the follow-up of patients who discontinued reslizumab are still incomplete.

Efficacy and Safety

A Phase III randomized placebo-controlled trial demonstrated that reslizumab significantly improved lung function, QoL, respiratory symptoms, and the number of asthma exacerbations, especially in patients with a late-onset asthma phenotype.[69–72]

Reslizumab improved lung function and reduced asthma symptoms after 2–3 days from the first infusion. These effects have been maintained for up to 24 months.-[73,74] Reslizumab was also effective in reducing OCS use, local and systemic eosinophilia.[75] Reslizumab was not effective in patients aged 12–17 years of age. Thus, studies in a pediatric population (< 12 years) were currently waived.[65]

Reslizumab is well tolerated. The most common side effects were infections, headache, worsening of asthma, and rarely local infusion-related symptoms. No cases of anaphylaxis have been described. No changes in the incidence of malignancies and mortality were noted in patients treated with reslizumab.[74]

Benralizumab

Mechanism of Action and Dosage

Benralizumab is a monoclonal antibody that specifically binds the IL-5Rα, reducing circulating eosinophils and modulating eosinophil-associated proteins and genes.[76] In the US, benralizumab was approved as an additional therapy for severe eosinophilic asthma in patients ≥ 12 years.[77,78] In Europe, benralizumab is recommended as additional therapy of severe uncontrolled eosinophilic asthma in adults, despite the high dosage of ICS and long-acting β2-agonists (LABA).[77,78]

Clinical, laboratory, and pulmonary functional features, such as pretreatment blood eosinophils count (≥ 300 cells/mm3), positive history of nasal polyposis, onset age at asthma diagnosis, forced vital capacity (FVC), exacerbation frequency, and OCS use, seem to be valid indicators of treatment response.[79,80]

The therapy is administered30 mg SC every four weeks for the first three doses, then every eight weeks.[81]

Efficacy and Safety

Two randomized, double-blind, placebo-controlled phase III trials showed a significant improvement in the number of asthma exacerbations, pretreatment FEV1, and asthma symptoms in adult patients treated with benralizumab compared to controls.[82,83] Data for children younger than 12 years of age are currently not available. Moreover, in a subgroup analysis of 108 adolescents aged 12–17 years, no significant effect on asthma exacerbation rates was noted (Fansera European Medicines Agencyhttps://ec.europa.eu/health/documents/communityregister/2018/20180108139598/anx_139598_en.pdf https://www.ema.europa.eu/en/medicines/human/EPAR/fasenra) The BORA phase III trial showed that 1–2% of patients in the benralizumab group experienced infections.[84] No evidence currently described malignancies or deaths due to benralizumab administration.[82,83,85]

Dupilumab

Mechanism of Action and Dosage

Dupilumab is a fully human monoclonal antibody, which blocks IL-4 and IL-13 receptors (Table 3).[86] Dupilumab is indicated asadditional maintenance treatment for patients with type 2 asthma characterized by high blood eosinophils and/or FeNO and inadequately controlled with high-dose of ICS plus another medication.[87,88] Dupilumab was approved in the US and Europe for patients aged ≥ 12 years with moderate-to-severe asthma and peripheral eosinophilia (≥ 300 cells/μL).[89] Dupilumab is subcutaneously administered 400 mg once, then 200 mg every two weeks, or 600 mg once, then 300 mg every two weeks.[89]

Efficacy and Safety

In three main clinical trials, dupilumab showed reduced severe asthma attacks, improved lung function, and reduced OCS use in adults and adolescents.[90,91] The QUEST trial reported that dupilumab significantly reduced the annual rate of asthma exacerbations in patients ≥ 12 years of age with uncontrolled moderate-to-severe asthma.[90] In particular, this positive effect was mainly observed in patients with high peripheral eosinophilia (> 300 cells/mm^3) and FeNO > 25 ppb.[90] Moreover, dupilumab significantly improved lung function and reduced the number of asthma exacerbations.[92]

Two-phase III ongoing trials (NCT02948959 and NCT03560466, respectively) evaluated the efficacy, safety, and tolerability of dupilumab in children aged 6 to < 12 years with severe uncontrolled asthma.[93]

Transient eosinophilia in the dupilumab group was reported in both QUEST and VENTURE trials and was not correlated with severe side effects.[91,94,95] The injection-site reactions occurred in 9% and 0% of adolescents treated with 200 mg and 300 mg of dupilumab.[93] In adults, cases of eosinophilic pneumonia and eosinophilic granulomatosis with polyangiitis have been described in the dupilumab group. Fortunately, these complications have not been reported in adolescents.

How to Choose the Best Therapeutic Option

The choice of the most appropriate biologic drug for asthmatic patients is a challenge for allergists. Firstly, pediatric allergists should assess the severity of asthma, excluding potential comorbidities and the poor adherence to inhalation therapy. Physicians should also characterize children with severe asthma, considering their phenotype (type 2 or non-type 2) and endotype (allergic or eosinophilic). Allergic severe asthma typically affects children with a clinical history of allergic rhinitis, positive skin prick tests, and high levels of total IgE (≥ 100 IU/mL) and FeNO.[96] In these patients, omalizumab may be currently considered the first therapeutical choice. Biological therapies with IL5/5Ra antagonists are generally prescribed in patients with severe uncontrolled eosinophilic asthma, which is characterized by peripheral eosinophilia (≥ 150 cells/μL).[96] Chan et al recently proposed an algorithm that may help physicians identify the best therapeutic option among the available biological therapies.[97] Based on this algorithm, patients with severe eosinophilic asthma may be first treated with IL-5 antagonists (mepolizumab, benralizumab, and reslizumab), effectively reducing asthmatic exacerbations. Eosinophils are the central driver of type 2 inflammation and play a crucial role in maintaining airway inflammation in patients that usually respond well to ICS.[8] In asthmatic patients, sputum eosinophilia predicts steroid response; however, sputum induction is not feasible in children, it is burdened with execution difficulties, and processing requires expertise and is time consuming.[8] Blood eosinophils have been shown to be significantly predictive of sputum eosinophilia, even with a lower specificity because of the influence of potential confounding factors (ie allergen exposure, parasitic infections, and current corticosteroid therapy).[8] Notably, OCS therapy may often reduce the peripheral eosinophil count in asthmatic patients.[98] However, Mukherjee et al have recently found that there is no correlation between sputum and blood eosinophils in a small group of adult patients with severe asthma treated with daily OCS.[99]

Dupilumab may be considered a first-line therapy in patients with severe asthma with FeNO ≥ 25 ppb and other allergic comorbidities, such as eosinophilic esophagitis, CRSwNP, and atopic dermatitis.

In our opinion, total IgE, blood eosinophil count and FeNO should be used as a surrogate of airway Type-2 inflammation among asthma patients and should be compositely considered when choosing an initial biologic agent for asthma treatment.

Conclusion

The introduction of monoclonal antibody agents in asthma treatment is a milestone in the application of personalized medicine. Since omalizumab was approved for asthma management, different biological therapies have revolutionized the therapeutical approach of severe uncontrolled allergic diseases in children and adolescents. However, comparative

studies are required to help clinicians choosing the best therapeutic option for patients with severe asthma who are eligible for more than one treatment. Moreover, standardized algorithms for the management of pediatric severe asthma should be realized, as already available in adults.

The research on asthma pathogenesis is ongoing and aims to improve the mechanisms driving the T2-high and T2-low endotypes. Identifying novel predictive biomarkers is a future goal in asthma management that may help physicians identify and select children and adolescents with severe asthma for innovative biologic therapies.

Acknowledgment

Martina Votto and Maria De Filippo are co-first authors.

Disclosure

The authors report no conflicts of interest in this work.

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