Biological Therapies for the Treatment of Severe Asthma in Children

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Abstract

Asthma is the most common chronic, non-communicable disease in paediatrics. It is a heterogeneous disease and several phenotypes are described according to symptoms, age of onset, triggers and response to treatment. The characterisation of the inflammatory mechanisms (molecular and cellular), also called endotypes, is more recent and led to the development of more targeted therapies for severe asthma in children, where conventional treatments are not sufficient. Based on the type of bronchial inflammation, there are two endotypes of asthma in children: high T-helpers 2 (TH2) and low TH2. The TH2 endotype is predominant in children, explained by a higher incidence of allergic sensitisation. Three biological therapies, acting on TH2 inflammation, benefit from an intervention from the National Institute for Health and Disability Insurance (NIHDI) in Belgium in children: omalizumab (anti-IgE), mepolizumab (anti-IL-5) and dupilumab (anti-IL-4 and IL-13 a-receptor). When administered in specific situations, these molecules can lead to a significant improvement in patients' symptoms and quality of life. Omalizumab is the best-studied biological therapy in children and is therefore preferred.

Introduction

Asthma is the most common chronic, non-communicable disease in children. In Western Europe, its prevalence varies from 7.4% (Austria) to 20.9% in the UK for children aged 6-7 years, with a prevalence of 7.5% in Belgium (1). For adolescents aged 13-14 years old, the prevalence varies from 8.3% (Belgium) to 31.2% in the Isle of Man (1). Asthma is a heterogeneous disease characterised by variable respiratory symptoms and airflow limitation, associated with inflammation and airway remodelling. The most common symptoms are cough, chest tightness, shortness of breath and wheezing. In children, asthma is most often manifested by recurrent bronchitis related to viral infections (2). Conventional treatment combines inhaled corticosteroids, short- and long-acting beta2-mimetics and anti-leukotrienes. In 5% of children with paediatric asthma, despite well-conducted treatment with high doses of inhaled corticosteroids in combination with other molecules, the symptoms persist and the asthma is classified as severe, leading to significant morbidity that necessitates sometimes the use of other more targeted therapies such as biological therapies (3). This article, after the description of a clinical case, provides a summary of the different biological therapies that benefit from an intervention of the social security (NIHDI) in Belgium and that are in use for children.

Case report

An 8 years old boy has been followed for several years in a paediatric pneumology clinic. Despite a well conducted treatment with anti-leukotrienes and high dose inhaled corticosteroids (500µg fluticasone propionate, daily) associated with formoterol (a long acting beta2-mimetic), he presents monthly exacerbations of viral induced asthma, with regular need for oral corticosteroids. He has been hospitalised several times. Between episodes, he presents rapid shortness of breath, frequent dry cough and symptoms of rhino-conjunctivitis. The biology shows a significant sensitization to dust mites (*Dermatophagoides Pteronyssimus 70.8kU/L, Dermatophagoides Farinae* 92.9kU/L), with a total IgE level of 244UA/L, and a blood eosinophilia of 220/mm3. Chest CT scan showed no bronchiectasis, bronchoscopy showed no anatomical abnormalities, bronchoalveolar lavage revealed predominantly lymphocytic inflammation, gastroscopy was normal, there was no immune deficiency, and the sweat test was normal. FEV1 was normal on breath function test. The asthma control score (ACT) was 10/27. Given the morbidity and severity of the symptoms, a biological therapy was started in February 2020 with Omalizumab at a dose of 150mg every 4 weeks, calculated according the weight and the initial IgE level. The first injections were given in the day hospital with monitoring for a few hours, and after 4 injections, the patient was given injections in ambulatory consultation. Since then, the patient has shown a clear improvement of his symptoms. He has not been hospitalized until now and didn't receive any more oral corticotherapy. He could practice sports without symptoms. He has never experienced any side effects from the treatment. His inhaled corticosteroid dose has been reduced by half. His ACT scores range from 22 to 27. He is still on Omalizumab and has been receiving it for 3 years. A discontinuation trial will be considered in the near future.

Discussion

Several clinical phenotypes of asthma are described according to symptoms, age of onset, triggers and response to treatment. The characterisation of inflammatory mechanisms (molecular and cellular), also called endotypes, is more recent and involves, in addition to the clinic, precise biological assessment and the use of biomarkers. In severe asthma in children, based on the type of bronchial inflammation, two asthma endotypes are distinguished: high T-helpers 2 (TH2) and low TH2 (4). The TH2 endotype is predominant in children, explained by a higher incidence of allergic sensitisation, ranging from 83% to 94% in children aged 6 to 18 years (5-6).

When pollutants, viruses or pneumallergens interact with immune presenting cells (dendritic cells), they migrate to the local lymph nodes where they activate naive TH cells, which in turn differentiate into TH1, TH17 or TH2 lymphocytes. Subsequently, in the TH2 endotype, TH2 lymphocytes secrete interleukin 4 (IL-4), which acts as a signalling intermediate between TH2 lymphocytes and B lymphocytes to increase

Table 1: Differential diagnosis of severe asthma.

Differential diagnosis	Complementary test
Tracheomalacia	Bronchoscopy, Rx trachea
Bronchopulmonary dysplasia	Chest CT, Spirometry
Tuberculosis	IDR, Quantiferon
Cystic fibrosis	Sweat test, genetic
Primary ciliary dyskinesia	Ciliary study, genetic
Bronchiolitis obliterans	Chest CT, Spirometry
Immune deficiency	Immune assessment
Foreign body inhalation	Bronchoscopy
Vascular Ring	Thoracic angioscan
Vocal cord dysfunction	ENT Fiberoptic nasopharyngoscopy
Exercise-induced hyperventilation	Exercise stress test
Hyperventilation syndrome	Psychological assessment

the production of immunoglobulin E (IgE). IgEs then bind to effector cells (mast cells, basophils and eosinophils) and trigger the release of histamine, leukotrienes and prostaglandins, which promote vascular permeability and smooth muscle contractility. In the airway epithelium, TH2 lymphocytes will secrete IL-5 and IL-13. IL-5 promotes eosinophil maturation and migration, while IL-13 induces mucin production by caliciform cells and modifies airway smooth muscle leading to hyperresponsiveness (2).

Severe asthma affects 5% of paediatric asthma patients. Severe asthma is defined by a high therapeutic pressure associated with clinical and/or functional criteria (7). Therapeutic pressure being a combination of high-dose corticosteroid therapy (Budesonide equivalent ≥800µg/d) and a long-acting beta2-mimetic and possibly anti-leukotriene or long-term systemic corticosteroid therapy. Clinical criteria are chronic respiratory pulmonary symptoms (respiratory symptoms ≥3 times/week ≥3 months) or exacerbations resulting in at least one intensive care hospitalization, at least two hospitalizations or at least two courses of oral corticosteroids within a year. Functional criteria are persistent severe bronchial obstruction with FEV1 Z-score <1.96 on a steroid test. In addition, three other parameters are required: the absence of another diagnosis (table 1), adequate management of precipitating factors, and good adherence and technique to treatment (3, 7-8).

A better understanding of the immunological mechanisms involved in the pathophysiology of asthma has allowed the development of more targeted therapies such as biological therapies. In Belgium, three treatments benefit from an intervention for the management of severe asthma in children: omalizumab, mepolizumab and dupilumab (6).

Omalizumab (Xolair®) is a monoclonal antibody that is specific for IgE. It binds to IgE and prevents the binding of IgE to FcεRI (IgE high affinity receptors present at the cellular surface) on basophils and mast cells, thereby reducing the amount of circulating IgE that can trigger the chain of allergic reactions, and allowing the reduction of blood and tissue eosinophils and inflammatory mediators, including IL-4, IL-5 and IL-13. It is administered to patients from the age of 6 years with allergic asthma, sensitised to at least 1 perennial pneumallergen and with high IgE levels. The dose and frequency of subcutaneous injections (every 2 and 4 weeks) depend on total IgE levels (in Belgium: 6-11 years: ≥200 - ≤1300; ≥12 years ≥76 - ≤700U/ml) and weight (9). It is the most well-studied molecule in children, resulting in improved asthma control, fewer respiratory exacerbations, reduced daily use of inhaled or oral corticosteroids, improved symptom control, and stabilisation or improvement of airway obstruction on breath function tests (6). In a randomised, double-blind study by Busse et al. of 419 patients aged 6-20 years, there was a 24.5% reduction in the number of symptomatic days and a 38% reduction in patients with at least one respiratory exacerbation (10). In the real-life study by Deschildre et al. of 78 children treated for 2 years, asthma control was observed in 80% of patients with an 83% drop in the rate of respiratory exacerbations. However, there was no beneficial gain in FEV1 (11). Response to treatment was observed within 4-6 months after initiation of treatment. Asthmatic patients with frequent exacerbators and with eczema or food allergies responded better in that study. Generally, the treatment was well tolerated. The main side effects are fatigue, arthralgia and hair loss. Anaphylaxis is rare. It is also indicated and benefit from NIHDI intervention in cases of sinonasal polyposis and chronic urticaria (8).

Mepolizumab (Nucala®) is a humanised monoclonal antibody which inhibits the biological activity of IL-5 by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the cell surface of eosinophils. Thus, it inhibits the IL-5 signalling pathway and reduces the production and life span of eosinophils. It is indicated in children aged 6 years in severe refractory eosinophilic asthma with a blood eosinophilia count of >300/mL at initiation and once in the 12 months prior to initiation. The dose is 40 mg in children aged 6-12 years and 100 mg in children aged ≥ 12 years, every 4 weeks, administered subcutaneously. Post-hoc analysis of 37 patients showed a significant decrease in the annual rate of respiratory exacerbation (6,12). There is only one paediatric study in children under 12 years of age. In this study by Gupta et al, administration of mepolizumab to 36 children aged 6-12 years confirmed a significant reduction in blood eosinophilia after 12 weeks, but the impact on asthma symptoms were not evoked in the report (13). Treatment tolerance was good and the main side effects described were injection site pain, headache, fatigue, respiratory infections and a paradoxical worsening of asthma. Mepolizumab is also indicated for the treatment of sinonasal polyposis, eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome (12).

Dupilumab (Dupixent®) is a humanised monoclonal antibody directed against the IL-4 receptor α, blocking the receptor shared by IL-4 and IL-5, which is essential for signal transduction. Dupilumab is indicated for the additional background treatment of severe oral corticosteroid-dependent asthma associated with type 2 inflammation, characterised by elevated blood eosinophils (≥150/mL eosinophils in the 12 months prior to and at the time of initiation of treatment) and/or an elevated fraction of exhaled nitric oxide (FeNO) (≥25ppb), in adolescents aged 12 years and older (6). The dose is 600 mg at the first injection, then 300 mg every 2 weeks. In the randomised phase III QUEST study dupilumab vs placebo, 107 adolescents aged 12-17 years were included. There was no significant improvement in the number of respiratory exacerbations. However, there was a significant improvement in FEV1 (14-15). For children aged 6-11 years and weighing between 15 and 60 kg, dupilumab is indicated for severe asthma associated with type 2 inflammation in patients who are inadequately controlled on high-dose inhaled corticosteroids in combination with another background asthma treatment. The dose is 300 mg every 4 weeks. In the VOYAGE study of dupilumab versus placebo in 408 children over 52 weeks, patients had fewer respiratory exacerbations (0.31 in the dupilumab group vs 0.75 placebo group) and improved lung function (+10.5%±1 dupilumab group vs +5.3%±1.4 in the placebo group) (16). The main side effects were injection site reactions, oropharyngeal pain and hypereosinophilia. Dupilumab is also indicated for the treatment of severe atopic dermatitis from the age of 12 years, eosinophilic esophagitis, nodular prurigo and sinonasal polyposis in adults (17).

In practice, the initiation of a biological therapy needs to be made by a paediatric pulmonologist working in an academic setting or an adult pulmonologist. The initiation of biological therapies should be discussed in a multidisciplinary meeting (paediatric and adult respirologist, allergist, ENT specialist, dermatologist, etc.) and a full differential diagnosis should be made before treatment is started. The treatment is initiated the couple

Table 2: Reimbursement criteria for biological therapies in Belgium for severe asthma.

Molecules	Action	Age	Common criteria	Specific criteria	Dose
Omalizumab	Anti-IgE TH2 high allergic asthma	≥ 6 years	- Medication review by a pharmacist or specialist nurse or physiotherapist - Daily high dose inhaled corticosteroid therapy combined with a long acting beta2-mimetic +/- anti leukotriene or long-term general corticosteroid therapy - At least 2 hospital admissions or 2 emergency department treatments for severe asthma in the previous 12 months, or at least 2 documented severe exacerbations in the previous 12 months (worsening of asthma requiring systemic corticosteroids for at least 3 days and/or hospitalization and/or emergency department visit)	Obstruction confirmed on spirometry ≥ 12 years Confirmation by prick test or RAST of perennial sensitisation IgE levels (children 6-11 years: ≥ 200 - ≤ 1300 IU/ml; >= 12 years: ≥ 76 - ≤ 700 IU/ml)	75 mg to 600 mg SC every 2 to 4 weeks depending on weight and initial IgE level
Mepolizumab	Anti-IL-5 Severe eosinophilic asthma	≥ 6 years		Blood eosinophilia ≥ 300/µL on two blood tests within a year	40 mg 6-12 years and 100 mg ≥12 years/ 4 weeks, SC
Dupilumab	Anti-IL-4Ra Severe type 2 asthma	≥ 6 years		Eosinophilia ≥ 150/µL on 2 blood tests within a year, associated with FeNO ≥ 25ppb Severe corticosteroid-dependent asthma ≥12 years	≥ 12 years: 600 mg first injection, then 300 mg every 2 weeks 6-11 years and weighing between 15 and 60 kg: 300 mg every 4 weeks

SC: subcutaneous.

of first times in an inpatient setting with monitoring of cardio-respiratory parameters for a few hours. It is injected subcutaneously into the outer arm by a third party. It can also be injected into the abdomen or the thigh. The reimbursement agreement will be valid for 4 to 6 months initially, and will be renewed for one-year periods thereafter. Table 2 summarises all the elements to be considered. If there is no significant response to treatment, it should be discontinued (6). There are few data on discontinuation of treatment. A discontinuation trial may be discussed after 3 years for Omalizumab. In case of relapse, the biological therapies can be restarted. In the real-life study by Deschildre et al., out of 100 patients, treatment could be stopped in 27 children after 25 to 86 months without relapse. Eight other patients had a recurrence of symptoms when omalizumab was stopped and had to be restarted (18).

Conclusion

The management of severe asthma in children and adolescents can be a therapeutic challenge. Patients with difficult to control or severe asthma should be referred to an expert centre. A better understanding of immune mechanisms has led to the development of targeted therapies to improve disease control when asthma symptoms persist despite maximum-dose inhaled corticosteroids combined with another molecule. Three molecules currently benefit from social security intervention in Belgium in children: omalizumab, mepolizumab and dupilumab. Omalizumab remains the best studied compound in children. Further randomised paediatric studies are needed to better define the role of biological therapies in the treatment of childhood asthma, and to determine cost-effectiveness, remission of disease and criteria for discontinuation of treatment, as well as indications for switching from one product to another. The choice of biological therapies should always be judicious and be discussed in a multidisciplinary meeting.

Conflict of interest

The authors declare that they have no conflicts of interest.

REFERENCES:

1. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006 Aug 26;368(9537):733-43
2. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018 Feb 24;391(10122):783-800. doi: 10.1016/S0140-6736(17)33311-1. Epub 2017 Dec 19.
3. de Blic J. Asthme. In : de Blic J, Delacourt C. Pneumologie pédiatrique. 2nd ed. Paris; Lavoisier;2018. 147-160.
4. Licari A, Castagnoli R, Brambilla I, Marseglia A, Tosca MA, Marseglia GL, et al. Asthma Endotyping and Biomarkers in Childhood Asthma. Pediatr Allergy Immunol Pulmonol. 2018 Jun 1;31(2):44-55.
5. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age. J Allergy Clin Immunol Pract. 2018 Mar-Apr;6(2):545-554. e4.
6. Epaud R, Giovanni-Chami L, Deschildre A. Biotherapies in severe asthma in children and adolescents. Rev Mal Respir Act, 2020; 12:2S27-2S34.
7. Lødrup Carlsen KC, Hedlin G, Bush A, Wennergren G, de Benedictis FM, De Jongste JC, et al. PSACI (Problematic Severe Asthma in Childhood Initiative) group. Assessment of problematic severe asthma in children. Eur Respir J. 2011 Feb;37(2):432-40.
8. Votto M, De Filippo M, Licari A, Marseglia A, De Amici M, Marseglia GL. Biological Therapies in Children and Adolescents with Severe Uncontrolled Asthma: A Practical Review. Biologics. 2021 May 5;15:133-142.
9. Omalizumab (Xolair®) prescribing information and summary of characteristics of products [Internet]. Gent, Belgium: Centre Belge d'Information Pharmacothérapeutique; 2015 [cited March 2023]. Available from www.cbip.be
10. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011 Mar 17;364(11):1005-15.
11. Deschildre A, Marguet C, Langlois C, Pin I, Rittié JL, Derelle J, et al. Real-life long-term omalizumab therapy in children with severe allergic asthma. Eur Respir J. 2015 Sep;46(3):856-
12. Mepoluzimab (Nucala®) prescribing information and summary of characteristics of products [Internet]. Gent, Belgium: Centre Belge d'Information Pharmacothérapeutique; 2020 [cited March 2023]. Available from www.cbip.be
13. Gupta A, Pouliquen I, Austin D, Price RG, Kempsford R, Steinfeld J, et al. Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. Pediatr Pulmonol. 2019 Dec;54(12):1957-1967.
14. Busse WW, Maspero JF, Rabe KF, Papi A, Wenzel SE, Ford LB, et al. Liberty Asthma QUEST: Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Dupilumab Efficacy/Safety in Patients with Uncontrolled, Moderate-to-Severe Asthma. Adv Ther. 2018 May;35(5):737-748.
15. Maspero J, Fitzgerald M, Pavord I, Wenzel S, Zhang B, Maroni J et al. Dupilumab reduces severe exacerbation rate and improves lung function in adolescent patients with uncontrolled, moderate-to-severe asthma: from the Liberty. Asthma Quest Study. Chest. 2018;154(4 Suppl):25A–27A.
16. Bacharier LB, Maspero JF, Katelaris CH, Fiocchi AG, Gagnon R, de Mir I, et al; Liberty Asthma VOYAGE Investigators. Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma. N Engl J Med. 2021 Dec 9;385(24):2230-2240.
17. Dupilumab (Dupixent®) prescribing information and summary of characteristics of products [Internet]. Gent, Belgium: Centre Belge d'Information Pharmacothérapeutique; 2022 [cited March 2023]. Available from www.cbip.be
18. Deschildre A, Roussel J, Drumez E, Abou-Taam R, Rames C, Le Roux P, et al. Omalizumab discontinuation in children with severe allergic asthma: An observational real-life study. Allergy. 2019 May;74(5):999-1003.