



Allergen-specific immunotherapy, novel drugs and biologicals: hopes from the difficult-to-treat allergic child

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Abstract In the last decades, significant progresses have been reached in the management of atopic diseases in childhood. Several approaches have been proposed in patients affected by moderate-to-severe atopic diseases. Severe asthma and atopic dermatitis are poorly known with different underlying phenotypes and endotypes, and they may require further cares with biological therapies. Omalizumab, anti-IgE monoclonal antibody, is effective and safe in patients with atopic diseases, especially uncontrolled asthma and chronic urticaria. Anti-IL-5 drugs including mepolizumab, reslizumab and benralizumab are effective in resistant eosinophilic asthma. In patients with uncontrolled atopic dermatitis, dupilumab is of benefit. Allergen-specific immunotherapy (AIT) represents the only treatment attaining immunologic tolerance and sustaining improvement in symptoms. Both subcutaneous and sublingual immunotherapies are characterized by a short-term and a long-term efficacy, as demonstrated by a reduced immunologic reactivity after discontinuation. Component-resolved diagnosis has been found an essential diagnostic tool potentially able to increase the efficacy of AIT in polysensitized children, establishing a precise AIT prescription for patient genuinely sensitized to

allergens. The future care of allergic diseases in childhood requires an individualized approach to achieve a patient-tailored therapy for difficult-to-treat atopic diseases.

Keywords Allergy · Atopic dermatitis · Children · Endotype · Immunotherapy · Severe asthma

1 Introduction

The incidence of allergic rhinitis (AR) and asthma is growing. Patients with severe AR, asthma, chronic urticaria and atopic dermatitis (AD) have a high social and economic burden with high prevalence of morbidity and extraordinary use of health-care resources. Severe respiratory allergies can be triggered by grass, tree, weed pollens, furry animals, mold, latex and foods of plant origin. Airborne allergens may interact with air pollution enhancing the risk of atopic sensitization and exacerbation of symptoms in sensitized subjects. Moreover, climate warming that has occurred over the recent decades (about 0.6 °C thus far) has dramatically advanced budburst in spring, therefore bringing forward the allergenic pollen season for spring-flowering taxa. We focus on recent significant developments in the management of atopic diseases in childhood.

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2 Asthma

Asthma is an umbrella term used for different diseases with varying mechanisms (endotypes) and diverse phenotypes identified by age of onset, triggers, clinical features, bronchial hyperresponsiveness (BHR) or airway inflammation. From a clinical perspective, two forms of asthma endotypes have been recognized (Lambrecht and Hammad 2015). About 80% of children and 50% of adults suffer from atopic asthma. A Th2 response precipitates an airway eosinophilic inflammation with increased eosinophils in the sputum and airways, and BHR. Patients have positive skin-prick test and/or serum immunoglobulin E (IgE) antibodies to aeroallergens and comorbidities including AR and AD. In non-atopic asthma, there is no IgE production to inhalant allergens and airway eosinophilic inflammation and BHR is induced by Th2 cytokines, such as IL-5 and IL-13, released by group 2 innate lymphoid cells. Non-atopic asthma includes a small number of patients with non-eosinophilic asthma in which airway inflammation may be neutrophilic, mixed granulocytic (both neutrophils and eosinophils, autonomously or simultaneously) or paucigranulocytic with no increase in eosinophils or neutrophils in sputum and airways. Non-atopic asthma is common in women, and it is associated with obesity, chronic rhinosinusitis and nasal polyps.

Anti-inflammatory drugs are the cornerstone of long-term treatment for asthma. In eosinophilic asthma, international guidelines recommend starting maintenance therapy with a low dose of inhaled corticosteroids (ICS). When asthma is uncontrolled with low to medium doses of ICSs and as-needed inhaled short-acting beta-agonists, inhaled long-acting beta-agonists (LABA) and/or leukotriene receptor antagonist are added. ICSs need to be administered twice a day apart from fluticasone furoate. Fluticasone furoate/vilanterol is a recently developed ICS-LABA combination for once-daily administration via a dry powder inhaler for patients aged 12 years and older. The once-daily therapy has the potential advantage over previous ICS-LABA twice daily dosing scheme to increase adherence which may result in better control of disease. Exposure to pollen contributes to the number of asthma exacerbations. Symptoms control upgrades with pollen predictions that allow the modulation of the therapy based on pollen counts.

Severe asthma is a heterogeneous rare disease in children. Several biomarkers have been described in the literature to assess asthma characteristics and their use can be helpful to predict the response to targeted therapies (Zinelli et al. 2009; Caffarelli et al. 2014). In severe asthmatic, disease control is poor despite of treatment with high-dose ICSs plus LABA. Besides oral CS, several emerging add-on therapies have been proposed for controlling severe asthma, including tiotropium and biologics.

Tiotropium bromide is a long-acting inhaled anticholinergic bronchodilator that is recommended as add-on treatment of tiotropium to ICS plus LABA for patients aged 12 years and older in the USA and for adults in Europe. Tiotropium improves lung function tests and reduces exacerbation rate among adults. In adolescents (aged 12–17 years), tiotropium increases lung function, but it does not affect symptoms and exacerbation rate, and there is a lack of agreement on optimal dosing (2.5 mg vs. 5 mg) (Hamelmann et al. 2016). Thus, in childhood, the role for tiotropium is unclear. Perhaps, it may help non-atopic children who do not benefit from agents for Th2 inflammation.

3 Biological therapy

In the recent years, interest has been increasing in precision or personalized medicine targeting the Th2 endotype to ameliorate management of patients with difficult-to-treat “Th2 high” asthma, AR, chronic urticaria and AD. Novel molecular-based treatments aim to provide long-term control of the disease and reduce steroid dose, abating adverse effects of corticosteroids. Many biologics are under investigation and four biological antibody-based treatments are nowadays available for asthmatics, one for chronic urticaria and one for AD.

Omalizumab is a humanized monoclonal anti-IgE antibody binding IgE Fc region that inhibits IgE binding to mast cells/basophils and the following inflammatory cascade. In children aged 6 years and above with uncontrolled moderate-to-severe asthma sensitized to perennial allergens, add-on treatment with omalizumab reduces exacerbation rate, improves quality of life and decreases the need for other controller medications (Mastrorilli et al. 2016a, b). Omalizumab is also approved for chronic spontaneous urticaria in patients aged 12 years and above. There

are “fast responders” with resolution of chronic spontaneous urticaria within 1–7 days after first dose (60–70%), “slow responders” with response after 3–5 months (10–20%) and “non-responders” (10–20%) (Metz et al. 2014). Symptoms usually return following discontinuation. Moreover, omalizumab has been shown to be a successful therapy for AR (Mastorilli et al. 2016a, b), AD and various forms of chronic urticaria, such as dermatographic and solar. Omalizumab is well tolerated, but it has the inconvenience of the subcutaneous administration every 2 or 4 weeks and elevated costs.

Anti-IL-5 drugs have been shown to be effective in refractory severe eosinophilic asthma (blood eosinophil count > 300 cells/mcl in the previous 12 months). There are two strategies. Mepolizumab and reslizumab bind to IL-5 blocking its effects. Benralizumab binds to the IL-5 receptor. All of them have been shown to reduce asthma exacerbation rate as add-on maintenance treatment. Mepolizumab and benralizumab are approved for 12 years and older in the USA and for adults in Europe, reslizumab for 18 years and older. Although there is some overlap, asthmatics who are eligible for treatment with mepolizumab, omalizumab or reslizumab, are often separate, highlighting heterogeneity of the disease (Albers et al. 2018).

Dupilumab is a monoclonal antibody binding to the common α -chain of the IL-4 receptor for IL4 and IL13 that blocks the effects of both IL-4 and IL-13. Dupilumab improves AD control, pruritus, anxiety and depression (Simpson et al. 2016), and it is approved for adults with moderate-to-severe AD candidate to systemic therapy. Moreover, dupilumab as add-on treatment has been shown to improve uncontrolled persistent asthma (Wenzel et al. 2016), and it has positive clinical effects in patients with nasal polyposis.

4 Allergen-specific immunotherapy

Allergen-specific immunotherapy (AIT) with standardized allergen extracts is the only causal treatment that may change the natural history of allergic airway diseases (Pajno et al. 2017). Both subcutaneous (SCIT) and sublingual AIT (SLIT) are effective in reducing symptoms and medication use in children with IgE-mediated asthma (Dhimi et al. 2017a, b) or

allergic rhinoconjunctivitis (Dhimi et al. 2017a, b). Improvements in rhinoconjunctivitis symptom-medication scores are sustained after interruption of AIT. Moreover, in children with AR, AIT prevents the development of asthma up to 2 years after treatment discontinuation and this effect seems to be persistent in long term, although it has to be fully demonstrated (Dhimi et al. 2017a, b). The safety profile of SLIT seems to be better than SCIT. It should be underlined the requirement for patients to have controlled asthma, because of greater risk of SCIT-induced adverse reaction in patients with unstable asthma. SLIT have been shown promising results in children with AD (Di Rienzo et al. 2014).

AIT effectiveness differs on patient selection, type of allergen, and product chosen for treatment. In the era of personalized medicine, further research should be conducted to individualize AIT using recombinant antigen technology. Component-resolved diagnostics may identify children who are genuinely sensitized to major aeroallergens rather than to cross-reactive molecules (Asero et al. 2015; Mastorilli et al. 2016a, b). Hence, the introduction of molecular diagnosis techniques is supposed to allow clinicians to better select patients for appropriate AIT prescription by improving the identification of the disease-eliciting pollen sources. Moreover, to achieve an accurate prescription of AIT, it is necessary to verify that respiratory symptoms are closely linked with high concentration of the pollen chosen in the preparation. Finally, AIT using single proteins to which the patient is allergic or modified proteins or peptides could increase its safety/efficacy.

5 Conclusions

The starting points of allergic disease point-of-care are avoidance of triggers, reliever and maintenance drugs, AIT and, the last but not the least, education of patient (Mastorilli et al. 2016a, b). Besides the chosen therapeutic management, adherence to therapy is a key factor for disease control. Communication and education of patients are mandatory to reach adherence and to empower management, under supervision of the physician. Numerous exciting advances have been reached on pediatric difficult-to-treat allergic diseases in the recent years. These innovations may lead to a more accurate diagnosis and a patient-

tailored therapy. This precision medicine represents the future of care in pediatric atopic diseases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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