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SUPPLEMENT ARTICLE

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New opportunities with biologic treatments in pediatric allergic and respiratory diseases

Laura Tenero | **Giorgio Piacentini**

Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Clinic, University of Verona, Verona, Italy

Correspondence
Laura Tenero, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Clinic, University of Verona, Piazzale Stefani 1, 37126, Verona, Italy.
Email: laura.tenero@aovr.veneto.it

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Abstract

In the last 20 years, the introduction of monoclonal antibodies has dramatically changed allergic diseases. At present, several monoclonal antibodies are approved for treating asthma, atopic dermatitis, chronic spontaneous urticaria, and chronic sinusitis with nasal polyps in children.

Biologics have also changed the management of these diseases in the pediatric population, tending toward personalized medicine based on the type-2 inflammatory pattern.

KEYWORDS
asthma, atopic dermatitis, biologic agents, children, chronic urticaria

1 | INTRODUCTION

Significant advances have been made in treating pediatric allergic diseases, opening a new way toward personalized medicine. Several biologics are now available for clinical settings, while others are still under investigation for pediatric use. The currently available biologic drugs act on specific key-cytokines of type-2 (T2) inflammation, such as interleukin (IL)-4, IL-5, and IL-13, and immunoglobulin E (IgE). Their mechanism of action consists of inhibiting precise molecular targets, modifying the natural history of allergic diseases in patients who do not respond to conventional treatments.

Allergic asthma, atopic dermatitis (AD), allergic rhinitis (RA), and esophagitis eosinophilic (EoE) are mainly supported by a T2 inflammation. Although clinically heterogeneous, these disorders share some common pathogenetic mechanisms. In this context, $CD4^+$ Th2 lymphocytes, type-2 innate lymphoid cells (ILC2), IL-4, IL5, and IL-13 play a crucial role in inducing and expanding allergic inflammation.

This brief review summarizes current evidence on available biological therapies to treat allergic diseases in children and adolescents.

2 | ANTI-IgE

2.1 | Asthma

Omalizumab is a monoclonal antibody that binds circulating IgEs, preventing their binding to the high-affinity receptors expressed on the surface of mast cells, dendritic cells, and basophils. Thus, omalizumab inhibits their activation and the subsequent release of inflammatory cytokines. Omalizumab was initially approved to treat severe asthma in patients ≥ 12 years. Then, its use was extended to children ≥ six years.[1] Several pediatric studies showed the efficacy and safety of omalizumab when administered as add-on therapy in patients with moderate-to-severe asthma, reducing the number of exacerbations and admissions to the emergency department (ED).[2] Furthermore, there was an improvement in lung function (FEV1), symptom control, quality of life (QoL), and reduced oral steroid use. Recent studies also 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.

The treatment with omalizumab can be proposed in children, with IgE <1500 UI/mL, skin test or *in vitro* positive for a perennial aeroallergen, inadequate control of respiratory symptoms (including nocturnal or frequent exacerbations) despite level 4 of GINA treatment. The dose and frequency of subcutaneously (SC) administrations are based on patient characteristics (body weight and serum IgE level).

Key Messages

The currently available biologic agents for treating allergic-respiratory diseases are particularly promising in the pediatric age.

2.2 | Chronic Spontaneous Urticaria (CSU)

Omalizumab was also approved for treating CSU with or without angioedema in patients ≥ 12 years with poor control of their symptoms, despite the optimized antihistamine therapy. Omalizumab acts blocking the mast cells' degranulation and the release of their inflammatory mediators. Currently, omalizumab is administered at 300 mg SC every four weeks in adolescents (≥ 12 years) and adults with CSU. The use of omalizumab in children < 12 years with CSU is under investigation.

3 | ANTI-IL-4R

Dupilumab is a humanized monoclonal antibody directed against the α-subunit of the IL-4 receptor (IL-4Rα), blocking the transduction signal mediated by IL-4 and IL-13. Dupilumab blocks the inflammatory cascade-mediated IL-4 and IL-13, reducing the development and progression of the T2 inflammatory pathway.[3]

3.1 | Asthma

Dupilumab is indicated in adults and adolescents (≥ 12 years) as an add-on treatment for severe asthma characterized by blood eosinophilia (>300 cells/L), high values (>20 ppb) of exhaled nitric oxide fraction (FeNO), poor control of respiratory symptoms, despite medium/high dose of inhaled corticosteroids (ICS) plus additional controllers including oral corticosteroids (OCS).

Clinical trials in adults and adolescents showed that dupilumab reduced asthmatic exacerbations, OCS use, and significantly improved lung function.[4,5] Dupilumab is SC administered 400 mg once, then 200 mg every two weeks, or 600 mg once, then 300 mg every two weeks.

Allergic rhinitis is a common comorbidity of asthmatic patients. Busse et al. demonstrated that dupilumab improved asthma control and QoL of patients with moderate-to-severe asthma and rhinoconjunctivitis.[6]

3.2 | Atopic Dermatitis (AD)

AD has a significant impact on the QoL of children and their caregivers. Initially approved in adults, dupilumab has been indicated to treat moderate-to-severe AD in adolescent patients (> 12 years). More recently, the FDA and EMA have approved the use of dupilumab also in children >6 years of age, as an add-on treatment of moderate-severe AD, poorly responsive to conventional therapies. The LIBERTY trials reported a significant efficacy and safety of dupilumab in adolescents and children with AD to reduce clinical scores.[3] Dupilumab showed similar side effects observed in the adult population. The most commonly reported side effects are related to the injection site (pain, hyperemia, swelling) and conjunctivitis. Unlike the adult population, the increase in viral skin infections and peripheral eosinophils was not reported in adolescents, confirming the pediatric group's more excellent tolerability of dupilumab therapy. Dupilumab showed persistence of clinical Efficacy and its safety profile in the long term (52 weeks).[3]

4 | ANTI-IL-5 AND IL-5R

In recent years, new agents have been studied to target T2 inflammation through the direct inhibition of IL-5 or IL-5R and the subsequent recruitment of eosinophils from the bone marrow. The currently approved biologics targeting IL-5 are mepolizumab, reslizumab, and benralizumab. Mepolizumab is the only available agent approved in children (≥ *6 years*) with severe asthma.

A multicenter study on asthma involving adults and adolescents with a history of severe eosinophilic asthma showed the Efficacy of mepolizumab in reducing the number of exacerbations, ED admissions, and hospitalizations.[7] Furthermore, the SIRIUS study, enrolling 135 patients with severe eosinophilic asthma, showed a significant reduction in the dose of ICS, number of asthma exacerbations, and an improvement of disease control.[8] The Efficacy and safety of mepolizumab have also been demonstrated for patients aged 6 to 11 years. A recent European multicenter open-label study of 29 children with severe eosinophilic asthma demonstrated a good safety profile even in the long term, thus confirming the use in the pediatric age.[9]In mild asthma, mepolizumab modulates both innate and adaptive immune responses, attenuates blood eosinophil count, without altering the distribution and activation status of lymphocytes, or the response against viral infections.[10]Mepolizumab is administered SC once every four weeks at a dose of 40 mg in children (6 to 11 years) and 100 mg in adolescents and adults. Mepolizumab is indicated as an add-on therapy of severe asthma with peripheral blood eosinophilia (≥150 eosinophils/MMC).

5 | CONCLUSION

Biologics have profoundly transformed the therapeutic approach of patients with allergic diseases, allowing tailored and personalized treatments. 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 choose the best therapeutic option for allergic patients eligible for more than one treatment. Identifying novel predictive biomarkers is a future goal in allergy management that may help physicians identify and select children and adolescents with severe allergic diseases for innovative biologic therapies.

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CONFLICT OF INTERESTS

Authors declared they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Laura Tenero: Writing-review and editing (equal). **Giorgio Piacentini**: Supervision (lead); Writing-review and editing (equal).

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