Type-2 inflammatory mediators as targets for precision medicine in children

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Abstract

The prevalence, heterogeneity and severity of type 2 inflammatory diseases, including asthma and atopic dermatitis, continue to rise, especially in children and adolescents. Type 2 inflammation is mediated by both the innate and adaptive immune cells and sustained by a specific subset of cytokines, such as interleukin(IL)-4, IL-5,IL-13, and IgE. IL-4 and IL-13 are considered signature type 2 cytokines, as they both have a pivotal role in many of the pathobiological changes featured in asthma and atopic dermatitis. Several biologics targeting IL-4, IL-5, and IL-13, as well as IgE, have been proposed to treat severe allergic disease in the pediatric population with promising results. A better definition of type 2 inflammatory pathways is essential to implement targeted therapeutic strategies.

The prevalence, heterogeneity and severity of in type 2 inflammatory diseases, including asthma and atopic dermatitis (AD), continue to rise, especially in children and adolescents, who are bearing the highest burden in terms of morbidity and health care expenditure.[1] Although allergen immunotherapy has disease-modifying properties and confers long-term clinical benefit after cessation of treatment, its indication is still limited to patients with clinically significant immunoglobulin E (IgE)-mediated respiratory allergies.[2] Most treatments available today merely provide long-term relief of symptoms, making it increasingly clear that new targeted approaches for the management of allergic diseases are required.

Type 2 inflammation is sustained by a specific subset of cytokines, such as interleukin (IL)-4, IL-5, IL-13, and IgE, resulting in the recruitment of cells such as eosinophils, basophils, and mast cells into the affected tissues.[1]

Type 2 responses are initiated with the disruption of the respiratory and, to a minor extent, epidermal epithelial barrier by exposures to allergens, viruses, bacteria, and other environmental triggers. Epithelial cells release IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which stimulate Th2 cells, type 2 innate lymphoid cells (ILC2), and invariant natural killer T cells (NKT cells) to secrete Th2 cytokines and to activate dendritic cells (DCs).[1] This results in further differentiation and clonal expansion of Th2 cells and activation of ILC2 cells, as well as tissue eosinophilia. Activated Th2 cells and ILC2 cells mainly release IL-4 and IL-13, which both have a central role in many of the pathobiological tissue changes, including airway inflammation and remodeling in asthma and epidermal barrier dysfunction in AD.[3] Additionally, mast cells, basophils, and eosinophils also secrete IL-4 and IL-13. Their biological functions are exerted through the binding of two receptor (IL-4R) subtypes, both sharing the common IL-4Rα.[1] IL-4R plays a key role in the IgE class-switch in B cells and the production of allergen specific IgE antibodies and in the activation

of other immune cells, such as mast cells, basophils, and macrophages. IL-13 and, to a lesser extent, IL-4 stimulate globet cell hyperplasia, increase mucus production and proliferation of smooth muscle cells in the airways; in the skin, IL-4 and IL-13 promote barrier dysfunction on epidermis by downregulating expression of filaggrin in normal keratinocytes, as well as increasing susceptibility to infections by inhibiting production of antimicrobial peptides.[1] In addition, it has been demonstrated that the chronic activation of the IL-4R pathway alters immunotolerance by promoting the complete subversion of Treg cells into Th2 cells, thus expanding and maintaining the type 2 inflammation.

Since IL-4 promotes the production of IgE, type 2 inflammation is related to elevated serum IgE and is generally associated with atopy in the pediatric age. IgE has a crucial role in allergic reactions, being implicated in both the early and late phase of allergic response.[4] IgE also has different immunomodulatory functions, including upregulation of IgE receptors, enhancement of mast cell survival, and promotion of Th2 cytokine expression.

Both IL-4 and IL-13 synergistically promote eosinophil migration to tissues.[1] IL-5, another key cytokine released from both Th2 cells and ILC2 cells, has a pivotal role in the induction, maintenance, and amplification of tissue and systemic eosinophilic inflammation. As mast cells and basophils, eosinophils produce a variety of cytokines and growth factors, including IL-5, capable of perpetuating this inflammatory vicious circle.[5] Upon activation, eosinophils release major basic protein (MBP) and other granule proteins, as well as lipid mediators and oxygen radicals, that result in epithelial damage, alteration of repair processes, and induction of fibrosis. These effects are mostly implicated in airway hyperreactivity and remodeling in asthma.[5]

With the increasing recognition of the role of type 2 immune responses in asthma and AD, several biologics targeting IL-4, IL-5, and IL-13, as well as IgE, have been proposed to treat severe allergic disease in the pediatric age. They include anti-IgE antibody (omalizumab), anti-IL-5 antibody (mepolizumab), and anti-IL4Rα antibody (dupilumab), the latter blocking the effects of IL-13 and IL-4 together.[5]

For children with severe therapy resistant asthma omalizumab, mepolizumab and dupilumab are all available options. Omalizumab is licensed for moderate to severe allergic asthma in patients [?] six years old.[6] Several randomized controlled trials and real-life studies have shown that Omalizumab reduces the rate of asthma exacerbations and hospital admissions in children.[7,8]By possibly increasing anti-viral response (IFN-α) from DCs, omalizumab also reduces virus-associated exacerbations. Omalizumab is generally well tolerated, with a low risk (0.1-0.2%) of anaphylaxis and injection-site reactions as the most common self-limiting adverse events (AEs).[9]

Children with severe eosinophilic asthma, who fail to respond or are not eligible to omalizumab, are the best candidates for a trial of mepolizumab. While extensive pediatric data are available for omalizumab, only 34 participants aged 12 years and older were included in the mepolizumab trials.[5] Mepolizumab reduced asthma attacks and hospitalizations and led to a reduction in dose of maintenance oral corticosteroids.[5] In the 6–11 years age group, safety and pharmacokinetic data are available, with only minimal efficacy data.[5] However, mepolizumab is currently licensed for severe eosinophilic asthma in children aged six years and over in Europe. A phase 2 trial (NCT03292588) is actively recruiting children to explore the effect of mepolizumab adjunctive therapy in preventing asthma exacerbations.

Dupilumab is the first biologic agent targeting both key cytokines of type 2 inflammation (IL-4 and IL-13) and is currently approved in adults and adolescents for use against moderate-to-severe AD and moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. Dupilumab is also licensed in adults only for severe chronic rhinosinusitis with nasal polyps.[1] The efficacy of dupilumab was first investigated in adolescents with moderate-to-severe AD. A clinically and statistically meaningful improvement was achieved in in adolescents receiving dupilumab rather than placebo. The most common AEs reported in the dupilumab group were injection-site reactions and conjunctivitis, the latter being well recognized AE of dupilumab in AD trials.[1] In dupilumab asthma trials, only 5,6% of recruited participants were aged 12–17 years. In these adolescents, dupilumab was shown to reduce severe asthma exacerbations, improve lung function, and reduce oral corticosteroid use compared with placebo. The only AE to have

occurred in the adolescent patient population was injection-site reactions, whereas conjunctivitis was not reported.[1]

Since evidence of type 2 inflammation is observed across multiple diseases beyond asthma and AD, dupilumab is being investigated as a potential novel treatment in other type 2 inflammatory diseases, such as allergic rhinitis, chronic rhinosinusitis with nasal polyps, and food allergy.[10] Clinical trials of dupilumab on adolescents and younger children with type 2 inflammatory diseases are ongoing, and their results are highly awaited.[1]

In conclusion, a better understanding of type 2 inflammatory pathways is essential to implement targeted therapeutic strategies in children with allergic diseases, such as severe forms of asthma and AD. Given that studies comparing different biologics are still lacking, there is the need for large pediatric trials, including children with type 2 diseases to expand efficacy data, explore safety issues, and identify predictive biomarkers of biologic therapies.

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