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The dawn of a new era for biological drugs in allergology

Mini Review

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SUMMARY

The emergence of biological drugs has transformed the management of severe allergic conditions, including asthma, atopic dermatitis, and eosinophilic esophagitis. Recently, the approval of omalizumab to treat multiple food allergies, in the United States, was a breakthrough in enhancing tolerance and reducing severe reactions. Dupilumab also shows promise in reducing IgE levels and symptom severity in patients with atopic dermatitis and food allergies, potentially offering a therapeutic avenue. Additionally, studies suggest dupilumab's role in mitigating the atopic march, especially in adolescents with early-onset and severe atopic dermatitis, raising questions about the optimal window for intervention and duration of treatment. The approval of dupilumab for children aged 6 months to 5 years opens avenues for further research on preventing the atopic march from infancy.

KEYWORDS: biological drugs, children, prevention, atopic march.

The emergence of biological medications in the realm of allergic conditions has fundamentally altered the approach to treating severe ailments that were once deemed nearly untreatable. This shift is particularly noticeable in addressing uncontrolled severe asthma, severe cases of atopic dermatitis (AD), and eosinophilic esophagitis [1,2]. Moreover, on February 15th 2024, the Food and Drug Administration (FDA) in the United States approved a supplementary application for the anti-IgE monoclonal antibody omalizumab, extending its use to treat both adults and children aged 1 year and older allergic to peanuts and at least two other foods, including milk, eggs, wheat, cashews, hazelnuts, or nuts [3,4]. This finding marks a significant breakthrough in addressing one of the primary goals for highly allergic patients: the possibility of increasing tolerance in patients with severe multiple food allergies, reduce the risk of severe and fatal reactions after accidental ingestion, and assure these patients and their families. This finding holds significant importance when considering that, specifically in adults, due to the age and severity of allergic reactions, the sole recommendation is to strongly avoid the food, including any traces, and carry adrenaline.

Living with a food allergy can be emotionally taxing, affecting not only the individual directly but also their loved ones. The constant fear of accidental exposure and the potential for severe reactions can create significant psychological burden. Anxiety levels may soar, leading to a heightened state of vigilance in navigating daily life. Simple tasks like dining out or attending social gatherings become sources of stress, as individuals must meticulously scrutinize ingredients and food preparation methods to avoid allergens. This perpetual sense of unease can erode one's quality of life, impacting relationships, work performance, and overall well-being. Moreover, the psychological toll extends beyond the individual with the allergy to their family members, who often share in the responsibility of safeguarding against potential triggers. Parents may experience feelings of guilt, anxiety, and overwhelm as they strive to create a safe environment for their allergic child. Siblings may grapple

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with feelings of resentment or jealousy, as family dynamics shift to accommodate the allergy.

Therefore, the effectiveness of omalizumab in enhancing tolerance in children and adults enduring persistent, severe food allergies such as peanut allergy [5], brings to light a new aspect: the opportunity to open an 'intervention window' in this patient category, where it is possible to make a therapeutic decision that affects both the allergological and psychological aspects, when previously their only therapeutic option was using adrenaline as needed.

A recent study indicated that dupilumab (an anti-IL-4 and IL-13 monoclonal antibody), may also offer therapeutic potential for individuals with AD and concomitant food allergies. In the study by Spekhorst et al. encompassing a cohort of 125 patients, median age 35.7 years, with AD and concurrent food allergies (33.6% to one, 28% to two foods,12% to three foods, 14.4% to four foods, 9.6% to five foods, 2.4% to six foods), in treatment with dupilumab, a consistent reduction in IgE levels across all food allergens was observed. Peanuts and hazelnuts emerged as the most prevalent triggering foods. This reduction spanned from 53.0% for peanut extract to 62.9% for apple after one year and from 80.5% for walnut to 86.9% for kiwi after three years of treatment. Additionally, while on dupilumab treatment, a total of 40 patients inadvertently consumed foods to which they were allergic, with 82.5% of these individuals reporting milder symptoms of food allergy [6].

If these findings are corroborated by randomized controlled studies in both adults and children, along with laboratory and clinical implications, dupilumab would emerge as a viable therapeutic avenue to increase tolerance in patients with food allergies and AD.

Recently, biological medications have increasingly played a pivotal role not only in treatment, but also in modulation and, surprisingly, prevention of allergic diseases. The progression of allergic diseases is called 'atopic march'. It typically starts with AD in infancy, followed by food allergies, allergic rhinitis, and asthma later in childhood [7,8]. In a recent study, Geba et al. discuss the moderating impact of dupilumab on the atopic march through a meta-analysis of 12 clinical trials. They evaluated the incidence rate ratios of newly emerged or exacerbated allergic events in patients compared to baseline and those in placebo groups in a period of 4-52 weeks. Their findings indicate an overall risk reduction of 37% for the development of new allergies, which increases to 54% when including IgE as a category. Notably, the most favorable response was observed in a specific patient profile: adolescents (aged <18 years) of Caucasian ethnicity, with early-onset AD (at age <2 years), severe AD, and pre-existing asthma [9]. Geba et al.'s study offers valuable insights and prompts numerous inquiries. Particularly in a predominantly adolescent subgroup with a distinct clinical phenotype, therapy using a biologic agent that targets T2 cytokines IL-4 and IL-13 shows promise in mitigating the progression of atopic comorbidities over the study period. This implies a level of flexibility in the T2 immune response throughout the progression of atopic conditions until adolescence, during which the response remains responsive to such interventions. Given the potentially increased predominance of the T2 immune response in younger patients, it could be hypothesized that the reduction effect seen in this study might be more significant when dupilumab treatment is commenced early in the disease process, such as during early childhood or infancy [10].

The preliminary results from these novel studies raise many questions: What is be the ideal 'intervention window' to prevent atopic march? What are the criteria to include patients? Can dupilumab also be used in patients who do not have severe AD, but mild AD, to prevent atopic march? Can it be inferred that therapeutic interventions for patients with food allergies are feasible until adulthood, whereas immune system modulation for prevention might be achieved until adolescence? How long should therapies with biological drugs for treatment and prevention be continued? Does discontinuation of the therapy result in the total or partial loss of the results achieved?

The approval of dupilumab to treat severe AD in children aged 6 months to 5 years by the FDA and the European Medicines Agency (EMA) can aid in the construction of large randomized controlled studies to prospectively assess the efficacy of dupilumab on the progression of the atopic march, starting from this age group where the immune system appears to be more plastic [11,12].

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Conflicts of interest statement

The authors declare that they have no conflict of interest.

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Ethical considerations

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