Allergen Immunotherapy in Atopic Dermatitis: light and shadow in children.

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Abstract

Atopic dermatitis (AD) is a chronic remitting-relapsing inflammatory skin disorder. Due to the multifactorial pathogenesis, there are numerous therapeutic management approaches, mainly based on symptomatic treatments. In recent years Allergen Immunotherapy (AIT) has been progressively advanced as targeted disease-modifying treatment of allergic disease. The most recent guideline from the American Academy of Dermatology concludes that data available do not support its use in AD. The Joint Task Force and The European Academy of Dermatology suggest that clinicians can consider AIT treatment in selected patients characterized by aeroallergen sensitization, prevalently HDM, severe AD, clinical exacerbation after exposure to the causative allergen. Nevertheless, its role in AD is still under debate, especially in children.

BACKGROUND

Atopic dermatitis (AD) is a chronic, remitting-relapsing inflammatory skin disorder that presents intense pruritus and varying degrees of recurrent eczematous lesions. In developed countries, the incidence seems to plateau at 10–20% in childhood and at 2-8% in adulthood.[1,2] The pathogenesis of AD is complex and not completely explained, caused by a combination of genetic and environmental factors. About 80% of AD patients have increased total IgE and is prevalently sensitized to aeroallergens, mainly house dust mite (HDM), defining the "extrinsic" form of AD. The remaining 20% has normal total IgE, referred to as the "intrinsic" endotype.[3] In overall 40–50% of children, AD is usually the first step of the so-called allergic march.[4] Due to the multifactorial pathogenesis, there are numerous approaches to therapeutic management mainly based on symptomatic treatments (moisturizers, topical and/or systemic corticosteroids, immunosuppressive molecules). Since recent years, many steps forward are being developed in the use of targeted disease-modifying drugs (e.g., omalizumab, dupilumab). In this context, Allergen-specific Immunotherapy

(AIT) is one of such pioneering therapies, introduced in clinical practice more than 100 years ago. Through a mechanism called tolerance, AIT is defined as the practice of administering slowly increasing amounts of the allergen(s) to achieve a hyposensitization, thus reducing the symptoms during the natural exposure to the allergen(s).[3,4] Efficacy of AIT is well documented in Hymenoptera venom allergy and allergic rhinitis (AR) and/or asthma, while its role in AD is still under debate, especially in children.

AIT and AD: OVERVIEW OF THE EVIDENCE

A large number of clinical studies were published to assess the clinical effectiveness of SCIT and SLIT in children with AD. Both routes of administration, subcutaneous (SCIT) or sublingual (SLIT), have been studied in AD and have been equally demonstrated to work through similar mechanisms.

The first encouraging study on applying SCIT in AD was published in 1974 by Kaufman and Roth.[5] Until the 2000s, several double-blind or not blind, randomized or not, placebo-controlled studies showed positive results on the efficacy of SCIT in children, but were conducted on small study's size.[5,6] In 2015 Lee et al.[6] retrospectively assessed 217 AD patients, aged 13-29 years old, treated with SCIT for at least three years. They observed the improvement of skin disease in 88.4% out of patients, a better outcome in patients younger than 12 years of age, in moderate/severe HDM AD. Also, Nahm et al.[6] described in an observational cohort study a favorable clinical response in 73.6% out of 251 patients, aged between 5 and 55, treated with HDM SCIT for 12 months.

In the 1990s, SLIT represented a significant step forward, particularly suitable for pediatric patients. Galli et al.[5,6]carried out the first placebo-controlled study using oral AIT in 60 children with AD sensitized to HDM. After three years of HDM oral AIT, the study did not reveal significant differences among groups.

The first double-blind, randomized placebo-controlled study was published in 2007 by Pajno G.B. et al.[5,6] They treated with HDM SLIT 56 children between 5 and 16 years old for 18 months. Among them, 28 children took SLIT in addition to standard therapy. A significant result was noticed in patients with mild-moderate AD, and, after nine months of treatment, the SCORAD index and amount of conventional therapy decreased in the active group than in placebo one.

Most of the subsequent studies confirmed the safety and efficacy of SLIT, although they were conducted on not standardized targeted populations and different AIT protocol schedule.[7]

In recent years many attempts to perform systematic review and meta-analysis on AIT in AD were made with a controversial conclusion, and no possible recommendation could be stated. Tam et al.[8] highlighted some methodological errors of the first meta-analysis conducted by Bae et al., due to the lack of blinding of outcome assessment, high post-randomization losses to follow-up, small study size, and inconsistency of findings allergens.[5,8] Also, Lee et al. in 2015 analyzed the most relevant trials in the literature and suggested the need for objective qualifying criteria about type and number of allergens, duration and schedule of therapy (rush or ultra-rush protocol).[9] Accordingly, Slavyanakaya et al., Cox et al., Ginsberg and Eichenfield did not warrant the use of AIT in children with AD and declared the need for well-designed RCTs that compare the efficacy of AIT with standard treatment in well-defined AD "phenotypes".[5, 10, 11] In this direction, Pajno et al. suggested that a more precise selection of clinical phenotypes (e.g., sensitization, comorbidity, cause-effect relationship between IgE-sensitization and AD exacerbation) may help to identify patients who could benefit from AIT.[12] Ridolo et al. proposed at least three criteria to select AD patient eligible to start AIT as an add-on therapy:(a)sensitization to aeroallergens, proven by skin prick test and/or IgE assay;(b)AD flare-ups induced by exposure to aeroallergens;(c) standardized type product for AIT must be chosen.[6]

In conclusion, the most recent guideline from the American Academy of Dermatology concludes that data available do not support the recommendation for its use in AD.[1] The Joint Task Force and The European Academy of Dermatology's suggest that clinicians can consider AIT treatment in selected patients characterized by aeroallergen sensitization, prevalently HDM, severe AD, clinical exacerbation after exposure to the causative allergen.[1,2]

LIGHT, SHADOW AND FUTURE PERSPECTIVE

Summary, AIT in children with AD cannot be used as first-line therapy, but it may be considered to reduce the progression of concomitant respiratory pathology as well as to prevent new sensitizations.[12]

As opposite to controversial evidence of effectiveness, safety of AIT was always one of the most important aspects to be carefully investigated since it was the primary reason to use this route. As a matter of fact, SLIT was introduced as a safer variant of SCIT to solve the rare problem of systemic reactions (SRs). Sublingual administration is well-tolerated, adverse reactions are predominantly local, and SRs are considered extremely rare and anecdotal.[13,14]Noteworthy, protocol doses schedule and type of product of AIT may influence safety; thus, moderate-dose of AIT and tyrosine-adsorbed HDM extract should always be preferred.[13,15] Moreover, considering that patients keep up improving after one year of treatment, future clinical studies should evaluate the long-term efficacy of HDM-AIT for at least three years.[6] Due to the duration and relatively high cost of immunotherapy, poor compliance is the principal reason for the failure of AIT. In a recent meta-analysis, Hankin et al. highlighted the evidence that AIT produced cost savings in place of conventional therapy, in both asthma and AR, in terms of fewer drugs used and fewer hospitalizations.[3] The main issue is the absence of biomarkers for predicting efficacy before and during treatment. Since the late 1990s, several attempts have been made to find biomarker candidates, such as cell adhesion molecules, chemokines or serological parameters, total or specific IgE, and IgG4-blocking subtype antibodies, but none of these is certainly reliable based on evidence.[5,6,12] In conclusion, several controversial points need to be clarified:

- eligible patients (e.g., age, type and severity of AD, type of sensitization, if perennial and/or pollen sensitization);

- route of administration of AIT (considering that SLIT should be preferred then SCIT in children);

- type of product of AIT chosen (standardized product should be preferred);

- duration of AIT course and age limit to start AIT (considering that AD have been shown to improve spontaneously throughout childhood and if AIT ;

- standard protocol schedule of administration for both SCIT and SLIT;

- cost-effectiveness ratio;

- clinical or immunological biomarkers for predicting efficacy.

Considering the lack of clear recommendations, starting AIT in AD patients should be decided by the pediatric allergist taking into account benefits, cost, possible risks, and the agreement of the patient/family that should be educated to ensure close adherence to AIT. Further researches are needed to recommend the proper use of AIT in AD for children.

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