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Allergen Immunotherapy and Atopic Dermatitis: Updated Guidance

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Introduction

Atopic dermatitis (AD), also commonly referred to as atopic eczema, is the most common chronic inflammatory skin disease. Research over the past 30 years has revealed that it affects approximately 13% of children and 7% of adults worldwide.[1,2] Among the growing number of treatment options for AD, the role of allergy to aeroallergens, such as house dust mite (HDM) pollens or animal dander, in driving this condition has remained uncertain for a long time. Consequently, so too has been the therapeutic role of allergen immunotherapy (AIT) for AD. The American Academy of Allergy, Asthma & Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI) Joint Task Force (JTF) on Practice Parameters recently updated their AD guidelines.[3] This update included a systematic review of the effectiveness and safety of AIT, including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) versus no AIT for patients with AD.[4] This article summarizes the systematic review findings, guideline update, and future directions.

Evidence

The previous practice parameter noted that AIT could be effective for treating AD. This guideline's linked systematic review evaluated 23 randomized controlled trials (RCTs; 11 SCIT trials and 12 SLIT trials) that included 1,957 adult and pediatric patients, with a median of study mean ages of 19 years, and a range of means of 4–34 years,[4] with, on average, a mostly baseline moderate-to-severe AD, with a median on the SCORing Atopic Dermatitis [SCORAD] scale[5] of 42, [0–103, indicating higher worse; a corresponding higher end of moderate severity using EASI being roughly 20], and a range of means of 12–64 (i.e. upper end of mild disease to middle range of severe disease, or roughly an EASI of 7 to 40). **Figure 1** presents the graphical abstract.

SCIT and SLIT comprised an approximately equal proportion of the included RCTs. Most studies focused on desensitized patients to HDMs; specifically, *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*. whereas 4 of the studies also included other inhaled allergens (e.g. pollens). Patients were mostly treated with standard topical therapy including topical corticosteroids and moisturizers with AIT added to the standard topical

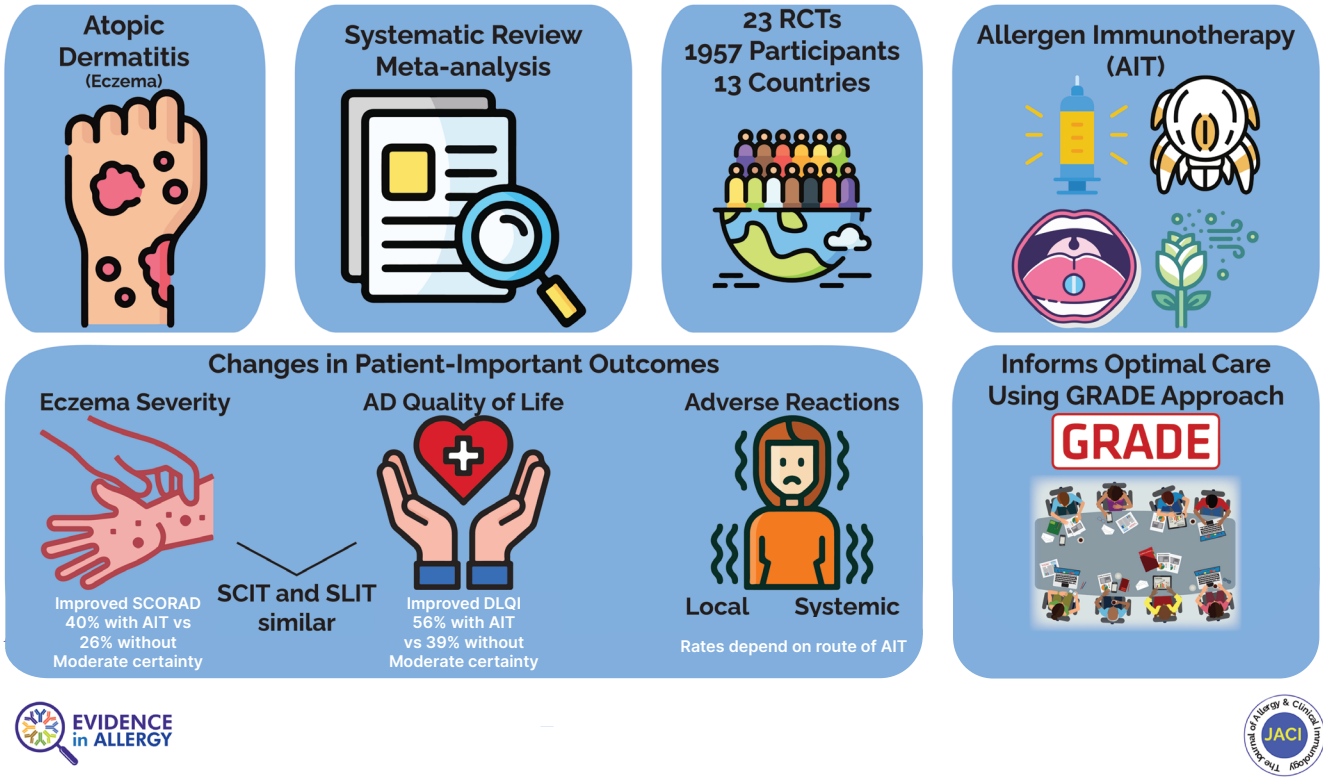

Figure 1. Systematic review and meta-analysis: allergen immunotherapy and atopic dermatitis; *reproduced with permission from Yepes-Nuñez JJ, et al. 2022.*

therapy. Furthermore, most studies included polysensitized patients in addition to those sensitized to HDMs. The studies added either AIT or no AIT (e.g. placebo) to standard care with topical treatments. AIT was administered for a median (range) of mean duration among studies of 12 (3–36) months. The trials were conducted in 13 countries across 4 continents (Asia, Europe, North America, and South America).

Based on a combination of clinician- and patient-reported AD severity (SCORAD), AIT likely improved AD severity by 50% or more from baseline compared with no AIT (40% with AIT vs 26% without AIT), with similar estimates of effect for SCIT and SLIT. AIT also likely improves quality of life (56% with AIT vs 39% without AIT, with a relative risk of 1.44 [95% confidence interval, 1.03-2.01], indicating a moderate certainty of evidence). Crude estimates of the median time-to-effect were 5 (range 1–12) months, and effects sustained over the duration of follow up stated above. The main adverse effects for this therapy were similar to those of AIT for allergic rhinitis and asthma, which are often transient.[6-10] In terms of common adverse reactions to AIT, which are also transient and usually minor, SCIT tends to increase local injection site reactions (mean of 66% of individuals) and SLIT tends to increase oropharyngeal itching (mean of 13% of individuals). Less common though more serious systemic reactions, or those severe enough to cause discontinuation of treatment, occurred in approximately 10% of those receiving SCIT, and rarely occurred in those receiving SLIT (0.14% of patients with a systemic reaction, 1.2% of patients discontinued SLIT).

Subgroup and sensitivity analyses were conducted using various statistical approaches to demonstrate that the results were consistent with the main findings. These variables included stratification by age, duration of AIT, the country where the study was conducted, the species of dust mite the patient was desensitized to, and whether the AIT was targeted at a monoallergen or a multiallergen, among others.

Mechanism

Allergens, such as HDM, may drive both innate and adaptive inflammatory processes and contribute to epidermal barrier disruption (e.g., intrinsic allergen enzymatic activity). These mechanisms stimulate the production of multiple cytokines including interleukin (IL)-4 and IL-13 from T-cells and local production of thymic stromal lymphopoietin (TSLP), IL-25, IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF) to collectively promote skin inflammation and itch.[11-13] Conversely, AIT works through several mechanisms including induction of IL-10 production by innate cells, epithelial repair, and modulation of the Janus Kinase Signal Transducer and Activator of Transcription (JAK-STAT) pathway. These mechanisms, along with other multiple anti-inflammatory, immunomodulatory, and protolerogenic effects, might explain the clinical benefits observed in the meta-analysis.[14-16]

Updated Guidelines

The JTF on Practice Parameters of the AAAAI and the ACAAI released updated guidelines for AD in December 2023.[3] The multidisciplinary guideline panel consisted of patients and caregivers, AD experts (dermatology and allergy/immunology), primary care practitioners (family medicine, pediatrics, internal medicine), and allied health professionals (psychology, pharmacy, nursing). The panel prioritized equity, diversity, and inclusiveness, and implemented management strategies to minimize the influence of conflicts of interest. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to inform the rating of the certainty of the evidence and the strength of the recommendations. Evidence-to-decision frameworks, subjected to public comment, translated evidence into recommendations using trustworthy guideline principles. The guideline's 25 evidence-based recommendations address the optimal use of **(1)** topical treatments, including barrier moisturization devices, corticosteroids, calcineurin inhibitors,[17] phosphodiesterase 4 (PDE4) inhibitors (crisaborole), topical JAK inhibitors, occlusive (wet wrap) therapy, adjunctive antimicrobials, application frequency, and maintenance therapy,[18] **(2)** dilute bleach baths,[19] **(3)** dietary avoidance/elimination,[20] **(4)** allergen immunotherapy,[4] and **(5)** systemic treatments, including biologics/monoclonal antibodies, small molecule immunosuppressants (cyclosporine, methotrexate, azathioprine, mycophenolate, JAK inhibitors), systemic corticosteroids, and ultraviolet (UV) phototherapy (light therapy).[21] The eAppendix of the guidelines provide practical information and implementation considerations for each treatment, presented in the form of 1–2 page handouts.[3]

In addressing one of the core questions in the guideline "Question 4. Should allergen immunotherapy be used for atopic dermatitis?", the panel agreed on 2 conditional recommendations. **Table 1** summarizes the implications of the conditional recommendations using the GRADE approach.[22] Likewise, each guideline recommendation is accompanied by the following: some common conditions that might influence whether the recommended course of action might be optimal, or not, for the patient; the systematically reviewed evidence for benefits and harms; the systematically reviewed patient values and preferences[23]; direct patient and family input addressing treatment of AD; factors that might affect accessibility, equity, and feasibility; implementation considerations; and a summary.

Recommendation 14

In patients with moderate-severe atopic dermatitis refractory, intolerant, or unable to use mid-potency topical treatment, the JTF panel suggests adding allergen immunotherapy to standard topical treatment over not adding (conditional recommendation, moderate-certainty evidence).

Conditions to consider:

1. Allergic comorbidities that will likely be responsive to immunotherapy (e.g., allergic rhinitis, or asthma with relevant sensitization) may lead to benefits for multiple diseases and therefore favour AIT.
2. Values and preferences regarding SCIT vs SLIT (e.g., convenience, age, travel plans).
3. The plausibility of allergen sensitization to reflect allergy. For example, a patient sensitized to horse dander with no further plausible exposure to horse dander will unlikely benefit from AIT to horse. In contrast, a patient with dust mite sensitization and dust mite exposure might benefit from AIT to dust mite.

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices, whether a conditional recommendation for or against a certain course of action, will be appropriate for individual patients (ie, the alternative strategy, in many scenarios, may be appropriate); clinicians must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Table 1. Interpretation of Strong and Conditional Recommendations; *adapted from Maleki-Yazdi KA, et al., 2023.*

Summary of Rationale: The panel inferred that most well-informed patients would value moderate-certainty benefits over little to no harms with SLIT, and their corresponding upsides and downsides (e.g. time commitment, resource use). With SCIT, the balance between benefits and harms is closer. With both interventions, the burdens and anticipated variability in values and preferences, particularly with age, severity of disease, and allergic comorbidities, contributed to the conditional recommendation.

Implementation Considerations: The available SLIT studies addressed SLIT in the form of drops, whereas most allergists in the United States may be most familiar with SLIT tablets. In Canada, SLIT tablets are marketed for dust mites, pollen from birch, grass, and ragweed pollen for allergic rhinitis. The age indications are as follows: dust mite tablets for 12 years to 65 years of age, birch tablets for 18 to 65 years of age, and grass and ragweed tablets for 5 years to 65 years of age. Separate AIT practice parameters state that there is no specific upper or lower age limit for initiating AIT if indications are present and after considering the absence of significant comorbid conditions and the patients' ability to complete AIT.[8] The guideline eAppendix[3] provides additional practical information and implementation considerations in the form of 1–2 page handouts.

Recommendation 15

In patients with mild atopic dermatitis, the JTF panel suggests against adding allergen immunotherapy to standard topical treatment (conditional recommendation, moderate-certainty evidence).

Conditions to consider:

1. Patients with allergic comorbidities with relevant sensitization that will likely be responsive to AIT (e.g., allergic rhinitis, asthma) may be more likely to pursue this treatment even if their AD is mild if it means that multiple conditions will improve. In contrast, most individuals with mild AD and no other allergic comorbidities will likely not pursue this treatment.

2. Values and preferences regarding SCIT vs SLIT (e.g., convenience, age, travel plans).

While the summarized evidence for benefits, harms, and contextual factors remained similar to those presented in Recommendation 14, the panel inferred that most well-informed patients would value avoiding the inconvenience of SCIT or SLIT. This preference is despite the moderate certainty for small benefits to AD outcomes in patients with mild AD. The anticipated variability in values and preferences, particularly with age and allergic comorbidities (e.g., mild AD but has indications for allergen immunotherapy due to indications for allergic rhinitis), contributed to the conditional recommendation.

The AAAAI/ACAAI JTF guidelines, as living guidelines, will continue to be updated and responsive to practice-changing evidence.

Future Directions Regarding Allergen Immunotherapy for Atopic Dermatitis

The impact of immunotherapy on some outcomes such as itch, sleep, and flares are less certain due to sparse data. Future studies should ensure that all patient-important outcomes are reported and that when collected, all measures are fully reported. Time-to-effect analyses are crude estimates, and future studies must formally address this issue. Future studies should clearly document whether systemic reactions after AIT for AD are immediate (e.g., anaphylaxis) or delayed (e.g., eczematous eruption or AD flare). No study has addressed AIT's potential long-term immunomodulatory effects (seen over 3–5 years of treatment). The systematic review provided sample size estimates that can be taken under consideration for planning future RCTs to address these now open questions. Additional research is also needed to better understand the mechanisms by which allergens and AIT affect AD, and how they might interact with the other factors to drive improvements and worsening of disease.

Conclusions

These findings support AIT's role in optimal AD outcomes and support a multidisciplinary model of care for patients with AD.

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