Pro/Con Review

Allergen Immunotherapy for Atopic Dermatitis: Is There Room for Debate?

Linda Cox, MD[a], and Moises A. Calderon, MD, PhD[b] *Ft. Lauderdale, Fla; and London, United Kingdom*

Allergen immunotherapy (AIT) is a disease-modifying intervention indicated for the treatment of allergic rhinitis (AR) and/or rhinoconjunctivitis, asthma, and Hymenoptera-induced anaphylaxis. Multiple placebo-controlled trials, systematic reviews, and meta-analyses have confirmed the efficacy of AIT in these conditions. Studies suggest that AIT may be beneficial in other allergic conditions, for example, atopic dermatitis (AD), food allergy, and large local reactions to Hymenoptera sting. With the exception of AD, the use of AIT in these other conditions is considered investigational.

AD has been included as a possible indication for AIT in individuals with aeroallergen sensitivity in US practice guidelines on AIT and AD.[1,2] Although the practice guideline recommendations are assigned an evidence rating B,[3] there continues to be debate about the effectiveness of AIT for AD.[4] One of the primary questions arising from this debate is which type of patient and which allergens are most effective in AIT for AD.

Is AIT effective for:

- *all patients with AD or certain subpopulations?*
- *all aeroallergens or only specific allergens such as dust mite?*

At the AAAAI 2015 Annual Meeting in Houston, Texas, we debated the current evidence in favor (pro speaker: Moises A. Calderon) and against AIT for AD (con speaker: Linda Cox). The objective of this paper is to present this debate, which focused on the clinical trials and systematic reviews of AIT for AD. We aim to provide some perspective for readers to better "weigh in" on this debate. The paper also includes the discussion of AD heterogeneity (eg, different phenotypes) and the efficacy of non-AIT interventions for AD, for example, medications and avoidance measures.

AD BACKGROUND

AD is a complex disease with a genetic predisposition influenced by innate and adaptive immune responses to a number of environmental factors including allergens, irritants, and microbes. Although referred to as a single disease, there is considerable heterogeneity in the natural history, clinical, and biophysical features of the disease, such that it has been suggested that different phenotypes and endotypes exist, in a manner similar to asthma and rhinosinusitis subgroups.[5] AD is characterized by genetic or acquired epithelial skin barrier dysfunction, which allows for the penetration of allergens and microbes into the skin. Immune dysfunction also plays a key role in AD pathogenesis. The majority of patients with AD have elevated serum specific IgE (sIgE) and/or positive skin test reactivity (SPT) to food or inhalant allergens. In some patients, aeroallergen exposure through inhalation or direct skin contact can lead to severe AD exacerbations.[6] It is believed that an inflammatory response is initiated when allergens on the skin are internalized by IgE receptor-bearing epidermal dendritic cells.[7] This relationship between aeroallergen exposure, inflammation, and AD disease activity suggests that there may be a role for AIT in the treatment of AD. Considering the heterogeneity of AD, it is unlikely that AIT would benefit all AD phenotypes and/or endotypes. Although most patients with AD have evidence of allergen sensitivity on blood or skin test, approximately 20% do not have sIgE or SPT to any inhalant or food allergens.[5] In addition, not all positive allergy (sIgE or SPT) tests are clinically relevant. Attempts to determine an allergen's clinical relevance can be challenging in individuals with persistent skin inflammation, particularly if the allergen is perennial. Unlike AR, where allergen sensitivity can be confirmed in an allergen environmental chamber or nasal provocation challenge, there are no validated tests to confirm the role of an aeroallergen in triggering AD.

HOW ARE AD OUTCOMES ASSESSED?

One of the challenges in evaluating the efficacy of AD treatment is the lack of a common standardized, validated outcome assessment tool. Generally, AD clinical trials utilize a scoring method that includes symptoms and examination findings. At present, there are more than 20 named instruments designed to measure the severity of AD.[8,9] The instruments vary in how each component is scored and weighed. Thus, it is difficult to compare the results of clinical trials utilizing different outcome tools to assess AD severity. To address this lack of standardization, an international collaboration, the Harmonising Outcome Measures for Eczema initiative, through a structured process of systematic reviews and international consensus, identified a core outcome measurement instrument for AD clinical trials.[9] The systematic review indicated that the Scoring Atopic Dermatitis (SCORAD) index and the Eczema Area and Severity Index (EASI) were the extensively validated and widely used instruments in AD clinical trials (see Figures 1 and 2 for example of the EASI and SCORAD scoring method).[10,11] The international consensus group, which included patients, health care professionals, methodologists, and pharmaceutical industry

[a]Department of Medicine, Nova Southeastern University, Ft. Lauderdale, Fla
[b]Imperial College London, National Heart and Lung Institute, Royal Brompton Hospital, London, United Kingdom
No funding was received for this work.
Conflicts of interest: The authors declare that they have no relevant conflicts.
Received for publication September 28, 2015; revised December 6, 2015; accepted for publication December 18, 2015.
Available online ■■
Corresponding author: Linda Cox, MD, Department of Medicine, Nova Southeastern University College of Osteopathic Medicine, 5333 North Dixie Highway, Ft. Lauderdale, FL 33334. E-mail: lindaswolfcox@msn.com.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2015.12.018

Abbreviations used
AD- Atopic dermatitis
AIT- Allergen immunotherapy
AR- Allergic rhinitis
DBPC- Double-blind, placebo-controlled
EASI- Eczema Area and Severity Index
GRADE- Grading of Recommendations Assessment, Development, and Evaluation
HDM- House dust mite
RCT- Randomized controlled trial
SCIT- Subcutaneous allergy immunotherapy
SCORAD- Scoring Atopic Dermatitis
sIgE- Specific IgE
SLIT- Sublingual allergy immunotherapy
SR- Systemic reactions

representatives, agreed on recommending the EASI as the preferred core instrument for the following reasons: it included only the 4 essential signs—erythema, excoriation, edema and/or papulation, and lichenification—and the severity is assessed at multiple body sites for each of the signs.

HOW EFFECTIVE ARE AD INVENTIONS AND MEDICAL TREATMENTS?

Avoidance measures

House dust mite (HDM) is the most common aeroallergen in AD and respiratory allergic disease. It has been estimated that as many as a third of AD patients with HDM hypersensitivity experience worsening of AD or respiratory symptoms with dust exposure.[12]

Interventions directed at reducing dust mite exposure might be expected to result in AD disease severity improvement. A Cochrane systematic review that searched databases through August 2014 for randomized controlled trials (RCTs) that assessed "... the effects of all house dust mite reduction and avoidance measures for the treatment of eczema" evaluated 7 studies (4 multiple interventions; 3 single intervention) that included 324 patients. Four studies assessed their primary outcome "… clinician-assessed AD severity with a named score" and no study provided information on the secondary primary outcomes—"caregiver-assessed quality of life."[12] The review found a modest treatment response in people with sensitivity to one or more aeroallergens, but noted the effectiveness of avoidance measures in the "…eczema population as a whole is unknown." In their conclusion, the authors state the "…very low-quality evidence" precluded them from making any clinical practice recommendations. At present, there is no substantive evidence that HDM avoidance measures lead to AD severity improvement in HDM allergic individuals.

Efficacy for medication treatments for AD

To date, none of the available medications for AD are disease modifying. Analogous to asthma treatments, current AD therapies are aimed at controlling symptoms and/or disease exacerbations, but none address the underlying cause. Limitations of medical therapies include incomplete and/or partial response and adverse effects and/or toxicity. A systematic review evaluated 12 different systemic treatments for moderate-to-severe AD in 34 RCTs that included 1653 patients.[13] The authors concluded "…the methodological limitations in the majority of trials prevented evidence-based conclusions." They determined that strong recommendations were only possible for the short-term use of cyclosporin A and it was "… impossible to make recommendations for mycophenolate, montelukast, intravenous immunoglobulins, and systemic glucocorticosteroids due to limited evidence."

ALLERGEN IMMUNOTHERAPY FOR ATOPIC DERMATITIS

Considering the limited proven efficacy of HDM avoidance measures and AD medication as disease-modifying therapies, we will proceed to debate the role of AIT in AD treatment. Our debate will begin by examining the findings of the systematic reviews and meta-analysis, which includes the strength of the evidence for AIT in the treatment of AD (Table I). The value of meta-analyses is that they combine several studies with small subject numbers to increase the power of the analysis, allowing for a more objective appraisal of the evidence than a traditional narrative synthesis of findings. A meta-analysis aims to quantify a pooled effect of the same outcome across different studies. Such statistical analyses are performed with the assumption that the studies included are sufficiently comparable in design, for example, similar patient populations, outcomes assessment tools, etc.[14] We will then explore the individual clinical trials to see what lessons can be learned (Table II). We will conclude the debate with a summary of unmet needs and recommendations for future investigations.

Most of the pitfalls described earlier in the paper regarding the clinical trial design of AD also apply to AIT trials. In general, there is considerable heterogeneity in AR and asthma AIT trial designs, with significant variability in key components that greatly impact the study's findings, for example, inclusion criteria, primary outcomes, and treatment duration. Recently, European and US regulatory authorities have provided guidance on AIT clinical trial design recommending the primary outcome assessment be the combined symptom-medication score.[15,16] This is consistent with the recommendation of the World Allergy Organization's (WAO) guidance document on appropriate trial design for AIT. The WAO Guidelines recommend that AIT products demonstrate at least a 20% improvement in combined symptom-medication score over placebo to be considered to be effective.[17] However, the requirement for a $\geq$20% improvement is not uniformly applied, as the Food and Drug Administration required a point estimate difference of -15% or more in the combined score over placebo for approval of the grass and ragweed sublingual tablets demonstration in 2014.[16,18,19] To date, the European Regulatory Authorities have not established a required magnitude of improvement for AIT product approval. The WAO's AIT guidelines do not specifically address AD, but they do suggest using a validated questionnaire, such as the Dermatologic Life Quality Index, if skin symptoms are being considered.[17]

AIT FOR AD CLINICAL EFFICACY: EVIDENCE FROM SYSTEMATIC REVIEWS AND META-ANALYSES

Pro: Moises A. Calderon

Over the last few decades, several clinical trials have been conducted assessing the efficacy and safety of AIT for AD. From these studies, only 9 were randomized placebo-controlled trials: 7 studies for subcutaneous allergy immunotherapy (SCIT) and