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ALLERGIC SKIN DISEASES (L FONACIER AND A WOLLENBERG, SECTION EDITORS)

Allergen Immunotherapy and Atopic Dermatitis: the Good, the Bad, and the Unknown

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Abstract

Purpose of Review In light of the recent advancements in atopic dermatitis treatment, this review aims to summarize the utility and efficacy of allergy immunotherapy in atopic dermatitis patients. We examine its mechanism, pathophysiology, cost-efficacy, and current guidelines for clinical practice.

Recent Findings The literature supports the use of allergy immunotherapy in atopic conditions such as allergic rhinitis and asthma but insufficient evidence exists to suggest its efficacy in atopic dermatitis. The use of allergy immunotherapy has been shown to provide long-term cost savings in both the USA and the European Union in certain populations but differences in prescribing patterns and manufacturing make it difficult to study its impact on a larger, generalizable scale.

Summary Conflicting meta-analyses data and conclusions highlight the need for better, higher quality research to better understand allergy immunotherapy utility in atopic dermatitis.

Keywords Atopic dermatitis · Allergy immunotherapy · AIT efficacy · Treatment

Abbreviations

AIT	Allergy immunotherapy
AD	Atopic dermatitis
AR	Allergic rhinitis
EASI	Eczema Area and Severity Index
FLG	Filaggrin
QALY	Quality adjusted life years
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SCORAD	SCORing Atopic Dermatitis

Introduction

Atopic dermatitis (AD) is an atopic chronic and relapsing skin condition that presents with varying degrees of eczematous lesions and pruritus. Skin barrier impairment and abnormal immune response are both critical in the pathogenesis of the disease. In recent years, several different treatment modalities have been investigated including topical steroids, systemic immunomodulatory agents such as biologics, small molecules, and allergy immunotherapy (AIT). As there is still a paucity of data as to the efficacy of AIT in AD patients, this review will summarize the recent literature on treatment efficacy, cost analysis, prescribing patterns, and barriers to treatment in both the USA and the EU.

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Atopic Dermatitis: Clinical and Pathophysiology Hallmarks

AD is a relatively common atopic skin condition that can present early in infancy and progress throughout adulthood. AD is characterized by genetic predisposition, *skin barrier* disruption, and an *aberrant immune* response (e.g., Th2 polarized) to environmental allergens. Clinically, patients typically present with intense pruritus and eczematous lesions with peculiar age-dependent distribution: facial and extensor eczematous lesions in infants and young children vs flexural eczema in older children and adults [1]. Further, though AD is primarily defined by clinical criteria, it is now accepted that

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AD subtypes can be distinguished based on their molecular and cellular characteristics [2••]. For example, 80% of AD patients have elevated IgE, referred to as an extrinsic endotype. The remaining 20% have AD but with normal levels of IgE, exhibiting antigen-specific IgE and referred to as the intrinsic endotype [3]. Patients with this intrinsic form show higher activation of TH17/IL-23 and TH22 and their related products [2••]. As such, mechanisms by which AD induces an immune response and consequently symptoms are being categorized into more specific groups, allowing for better and personalized therapies.

To understand the impact of the most recent changes in therapy of AD requires an understanding of the biological hallmarks and pathophysiology of the disease. In essence, AD is a chronic and relapsing form of atopic skin inflammation that is driven by a combination of penetrating allergens (impaired skin barrier), abnormal T cell sub populations, and inflammatory cells such as eosinophils, mast cells, and dendritic cells all working together to induce an allergic response. The role of allergen sensitization in AD pathogenesis has been investigated, but remains to be fully elucidated. In certain subgroups of sensitized patients, exposure to food or aeroallergens exacerbated AD symptoms [4]. AD patients tend to have higher levels of total serum IgE, leading to sensitizations to foods which are usually not associated with symptoms upon ingestion [5, 6]. As a result, the gold standard for proving a diagnostically relevant determination of sensitization for foods is a challenge test with the allergen in question [2••].

Understanding these pathophysiological processes has become increasingly important as the burden of AD has been increasing throughout the industrialized world, with an estimated 5–20% of the world's population suffering from this disease [7]. In one EU study, even with current treatment, over half of the study population who suffered from the disease experienced significant impact on their daily lives with "problems with intimacy," "guilt," and "shame" appearing universal across the population [7]. A staggering 88% of participants with severe AD reported the disease as preventing them from facing life [7]. Interestingly, the prevalence distribution of AD varies wildly across the globe with less than 2% of cases in Iran versus 16% in Japan and Sweden in children ages 6–7 and less than 1% in Albania to over 17% in Nigeria in children ages 13–14 [8]. Overall, higher prevalence of atopic eczema is reported in Northern Europe whereas the lowest prevalence is associated with Eastern Europe and Asia [8]. To further compound this issue, having one atopic condition is associated with an increase in prevalence of other atopic conditions. Children with eczema, for example, have a higher prevalence of asthma, increased asthma severity, allergic rhinitis, and an increase in rhinitis severity. Eczema is also associated with an overall fivefold higher prevalence of food allergies in children [9]. Oftentimes, individuals suffering from AD (and their caregivers) end up with greatly diminished quality of life due to sleep loss, reduced productivity, cosmetic concerns, and chronic/relapsing skin irritation and pain [10]. Additionally, AD patients have an increased occurrence of depression, anxiety, and even increase risk of overall hospitalizations [1].

Although considered to be primarily a disease that originates in infancy and progresses through life, a recent meta-analysis reveals that 1 in 4 patients had an adult-onset of AD [11]. This further accentuates the need for research into the origination of the disease and whether the different times of onset ultimately result in different biological processes and appropriate treatments.

Overview of AD treatment

Until recently, the best that physicians could offer to manage AD was to recommend adequate skin hydration, topical ointments, and the avoidance of triggers including allergens (if known) and emotional stressors [12]. The treatments for AD were primarily centered on the use of topical corticosteroids and/or immunomodulators and for moderate to severe cases systemic immunosuppressants [13] and/or UVA/UVB light therapy [14]. In addition, some physicians recommended antihistamines in spite of discouraging recommendations [14]. These agents did not prove highly effective and did not come without side effects. One recent study of such side effects showed that topical corticosteroid use may be associated with the development of type 2 diabetes [15]. As an attempt to avoid or minimize the side effects associated with long-term use of topical steroids and for a long-term management of flares, many physicians consider proactive therapy with TCS and/or TCI. The idea of this therapeutic approach is to continue to use topicals (either TCS or TCI, usually twice a week) to previously affected areas to control sub-clinical inflammation resulting in the reduction of flares and improved quality of life for the patients [14].

As the molecular basis for AD has become increasingly understood, the development of more specific and targeted therapies has become possible. Several studies have pointed to skin barrier dysfunction as a crucial part of AD disease initiation. In 2006, a seminal work by Palmer et al. demonstrated that inherited reduction or loss of filaggrin (FLG) expression as a major predisposing factor for human AD and asthma (in patient with AD) [16]. This was the first study demonstrating a link between the expression (or lack of expression) of a skin barrier protein (*i.e.*, FLG) and the risk of AD. Although, the role of FLG deficiency in AD is still under investigation, several studies are now investigating FLG replacement strategy as a treatment option in AD.

Other agents have targeted the AD immune response. Crisaborole, a topical boron-based PDE4 inhibitor, has been

approved by the FDA in 2016 for the treatment of mild-to-moderate AD [13]. A recent meta-analysis showed that crisaborole effectively reduced lesion size, investigator-assessed clear skin, and was not associated with any adverse events when compared with placebo [17]. By inhibiting PDE4, crisaborole allows for better control of cellular inflammation, blocking the release of cytokines and preventing downstream signaling of nuclear factor-kB [18–20]. More recently, biologics targeting Th2 inflammation have been developed. Dupilumab (Regeneron and Sanofi) which has enjoyed the most success, gaining FDA approval in 2017 for the treatment of adults with AD, is a fully human monoclonal antibody that targets the IL-4 receptor α subunit that blocks the signaling of both IL-4 and IL-13, which are key cytokines in the Th2 immune response [21]. More recently, the indication for dupilumab has been extended to asthma and chronic nasal polyposis both in the US and the EU.

Targeting of other "allergic" biologic markers effectively used for other atopic disorders, such as IL-5 (mepolizumab; approved for severe asthma), IgE (omalizumab; approved for asthma and chronic idiopathic urticaria), or PGD2 (timapiprant, CRTH2 antagonist) have not yet shown statistically significant results in RCTs when used for AD [13, 22, 23]. Interesting small-scale studies with omalizumab indicated responders were non-FLG-mutation carriers, indicating that patients with a primary skin barrier deficiency are less likely to benefit from an immunomodulatory therapy with anti-IgE [24]. Exciting results have been reported from a phase 2b study using the topical JAK inhibitor, ruxolitinib in AD, showing a significantly improved EASI score in the ruxolitinib cream 1.5% twice at day versus vehicle at week 4 [25•].

Despite these advancements in AD treatment over the past decade, there is still a dearth of research and options for patients with refractory disease or for those with specific environmental triggers.

The role of allergy immunotherapy in AD armamentarium is still highly questionable mostly due to the lack of solid trials. As we proceed with a more personalized approach of treatment, we wonder if allergy immunotherapy (AIT) could be considered a viable solution to help fill in those therapeutic gaps in at least a subset of AD patients. This review compiles current knowledge regarding the role of AIT in the management of AD and identifies areas of insufficient information to be explored in future investigations.

History of Allergen-Specific Immunotherapy

Over the past several decades, emergence of new therapies for allergy-induced disease has fundamentally altered the way that we approach and think about allergic disorders. Allergy immunotherapy (AIT) is one of such pioneering therapies and has been used to help control and minimize allergic symptoms in a variety of patients. Defined as the administration of slowly increasing doses of specific allergens, its target is to control IgE-mediated disease. Along with the use of biologics targeting TH2 inflammation, allergic disease(s) can be controlled through prevention of mast cell degranulation [26], inhibiting IL-4-secreting T cells [27••] and inducing B cell tolerance [28]; AIT increases the production of IL-10 and TGF-β in regulatory T cells is thought to contribute to regulatory T cell function and immunoglobulin class switching to IgA, IgG1, and IgG4. These, in turn, compete with IgE for allergen binding, decreasing allergen capture and presentation and ultimately reducing the allergic response [27••].

The idea of immunotherapy dates back thousands of years. One of the earliest mentions of immunotherapy is when King Mithridates of Pontus attempted to use snake venom to make himself immune to the toxin [7]. Within the modern era, credit is given to Leonard Noon who, in 1911, injected patients with hay fever with serial dilutions of grass pollen–derived allergen extracts, otherwise referred to as subcutaneous immunotherapy (SCIT) [29]. In the 1950s, the first clinical trials with AIT were performed by William Frankland, who demonstrated that hyposensitization was more effective with high doses compared with low doses for patients with hay fever [29]. Soon, allergen extracts were combined with adjuvants such as monophosphoryl lipid (MPL), aluminum hydroxide (Alum), and calcium phosphate, with MPL showing promising results as a vaccine to grass-, tree-, and ragweed pollen–allergic patients [30]. As the allergy extracts and their accompanying adjuvants became more refined, the discussion soon turned to modalities of AIT delivery. The classical method, from Noon onward, has been subcutaneous injection but efforts to create oral and nasal delivery mechanisms have propagated. Recent data and meta-analysis have shown that sublingual immunotherapy (SLIT) is a viable alternative to SCIT and has been shown to reduce symptoms of allergic rhinitis [31]. Similarly, SLIT has been shown to improve dust mite–sensitized children with mild-moderate atopic dermatitis [32]. Since SCIT requires an injection-based administration, SLIT may provide patients reluctant to such treatments a viable alternative. However, both SCIT and SLIT have seen low overall therapy compliance as well as varying levels of treatment literacy. In one meta-analysis, SCIT discontinuation ranged from 6 to 84% whereas SLIT discontinuation ranged from 21 to 93% [33]. Patients' knowledge regarding the duration of treatment has also been shown to be poor with one study reporting 60% of patients unaware of optimal treatment duration and only 10% expecting to be on therapy for several years [34].

Therefore, more research into the barriers of treatment adherence is necessary to improve overall patient outcomes and compliance. Other concerns in comparing SCIT and SLIT in clinical practice include overall efficacy where SLIT has been

shown to be less effective in symptom reduction in conditions such as allergic rhinitis. One study even suggested that a large portion of SLIT effects could be attributed to the placebo effect [35].

AIT: Updates on Prescribing, Payments, and Preferences

Healthcare Costs and Fiscal Barriers

As more research is conducted surrounding the efficacy of AIT in AD, we must examine the financial barriers to its implementation as well as the potential cost-savings associated with its use in place of other alternatives. The two forms of AIT are divided into two groups for comparison, SCIT and SLIT.

As the use of AIT in AD is still limited in clinical setting, we can use specific immunotherapy in other diseases such as allergic rhinitis and asthma for cost comparisons to better understand the potential impact on AD. The first of such studies for SCIT was conducted in the 1990s in Germany by Buchner and Siepe, reporting a 54% reduction in direct and indirect costs in patients with allergic rhinitis (AR) and asthma when compared with traditional symptomatic drugs [36]. In 2005, an economic analysis from Denmark in AR patients with grass pollen or mite allergy demonstrated more than a twofold decrease in cost per patient/year after AIT [37]. Similarly, in 2007, a French cost analysis showed that AIT vs current symptomatic treatment yielded €393 in savings for dust mite allergies and €1327 for pollen allergy in adults with AR. In children, those savings were €583 and €597 respectively. One of the largest studies on this topic used Florida Medicaid claims data on newly diagnosed children with AR. Patients who received AIT used less drugs, had fewer outpatient visits and inpatient admissions, and used less resources in 6 months after AIT vs before AIT [38]. Overall, the study found that the mean 6-month saving was $401.

As SLIT tablets have become available, they have naturally been the subjects of economic analysis. One of the first studies was conducted in Milan (Italy), with researchers finding a substantial reduction in all outcome measures (e.g., number of exacerbations, medical visits, and absence from nursery or school) during SLIT for patients with AR [39]. Similarly, two studies examining the cost-effectiveness of grass allergen SLITS tablets in EU measured quality adjusted life years (QALY) and the cost per QALY gained. According to the UK's National Institute for Health and Clinical Excellence guideline, a drug that can generate one QALY for less than €29,200 compared with its alternative is considered cost-effective [40]. In both studies of Northern and Southern Europe, grass allergen tablets were able to meet that guideline, proving to be cost-effective options for patients with AR [41, 42].

Many of these studies were then further examined in a meta-analysis by Hankin et al. in a recent review. They found compelling evidence that AIT produces cost savings, both as SCIT and/or SLIT, over symptomatic therapy in both asthma and AR [43]. Studying the use of AIT in non-AD atopic conditions can provide us with clues as to its cost-effectiveness and promote their study and use in AD populations which would help improve patient care outcomes and overall healthcare cost. As useful as these analyses for AR and asthma are, they are limited in their ability to discuss cost-effectiveness in AD, and additional research must be conducted to determine whether AIT is truly a viable alternative to other modern therapies.

European and American Providers and their Preferences

Given the growing base of literature on the economic feasibility, clinical outcomes, and safety profile of AIT, one might expect similar prescribing patterns and attitudes among providers in the USA and the EU. Surprisingly, differences in manufacturing and development, regulatory requirements, diagnostic approaches, and clinical administration all contribute to the differences between the US vs. EU use of AIT [44••].

Starting with the manufacturing, the US focuses its standardization of allergen extracts on the extraction method rather than the collection of source materials. This has created a discrepancy between different types of extracts with pollen source material being well standardized with an industry-wide accepted collection process and a uniform extraction compared with fungal extracts that enjoy similarly ubiquitous extraction processes but widely varying source materials such as strain and growth medium [44••]. This therefore results in widely varying extract quality and has precipitated a push for further standardization focusing on a common potency unit but these plans have yet to be implemented. In the EU, each European manufacturer used in-house references and assays for the extraction process. This means that standards of potency and extraction for all products are based on the references used for the most common allergens. In 2001, the CREATE project was funded by the EU to push towards cross-product comparability and allergen standardization. This was followed up with the BSP090 project in 2014 to establish recombinant major allergens as reference standards to be used by all manufacturers. To date in the EU, the use of these standards is still optional.

Regulatory standards in both the USA and EU further compound this issue of inadequate standardization. The FDA originally devised three categories (I, approved; II, not approved; III, insufficient data) to classify the allergen products [45]. While categories I and II have clear parameters, category III has led to a group of products that have insufficient evidence as to their efficacy but are still allowed to be put on the market

[45]. This further exacerbates the issue of non-standardization by further obfuscating which products could reliably have an effect on patient outcomes. The FDA has attempted to eliminate category III and reclassifying all products into the I and II categories but has failed to completely do so [44••]. In the EU, legislation provides a framework for the member states but allows each member state (MS) to regulate the specifics at the national level. Although all allergens are considered medicinal products and subject to standard drug regulations, proving a positive benefit/risk ratio, member states can choose to exempt products from this standard procedure known as marketing authorization (MA). This has created a highly complicated situation in which each member state can exempt allergens personalized for patient needs, termed named patient products (NPP). Denmark and Sweden do not have such exemptions, while Spain, Portugal, and France allow such exemptions and also have the largest market share of these products. NPPs therefore do not have to abide by these drug requirements whereas the typical AIT products do [44••].

Thirdly, diagnostic evaluation standards between the USA and the EU result in different practice patterns and use of AIT. In the USA, skin prick testing is the primary tool to confirm IgE-dependent aeroallergen sensitization [44••]. Other testing such as intradermal testing or specific IgE tests are used as confirmatory tests or as supplements to percutaneous skin tests but are not as frequently employed as skin prick tests [44••, 46]. Nasal or conjunctival challenge tests may also be used to identify clinically relevant allergens [47]. This is in contrast to EU where detecting allergen-specific IgE in vitro is much more common in clinical practice. Further prerequisites for AIT use in both the EU and the USA are the availability of high-quality allergen extracts and there must be demonstrated efficacy in that patient subpopulation [48].

All of these aforementioned differences between the USA and the EU contribute to widely varying practice patterns and recommendations by the different regulatory bodies. For example, clinical trials with house dust mite (HDM) SLIT have been shown to control symptoms and reduce overall exacerbations in both allergic rhinitis and allergic asthma [49]. In Europe, as per the Global Initiative for Asthma guidelines, HDM SLIT tablets are recommended in the treatment of allergic asthma. Yet, no such approval exists for HDM-related asthma in the USA. Similarly, sublingual drops are used in an off-label capacity in clinical practice in the USA despite a lack of FDA approval and double-blind placebo-controlled studies [44••]. Within the EU, there are many differences across the member states. In Germany, SCIT is preferred. SLIT is common in France and Italy but much less so in Spain. Because of the significant variety of potency, extraction methods, and regulation, product-specific evaluations have been recommended to create clinical guidelines that can be adopted by all practicing physicians [41, 44••, 47].

AIT and AD: When to Prescribe and Other Guidelines

After having discussed the cost-effectiveness, barriers, and clinical perception of allergy immunotherapy amongst providers, we must finally look at what the current state of the art in using AIT in AD.

In recent years, there have been multiple articles suggesting the efficacy of AIT in AD, although the topic is still highly controversial. One paper by Caraballo et al. showed that the AIT-treated group with AD saw a statistically significant improvement over control group in SCORAD as well as a reduction in overall oral steroid use [50]. The study analyzed 60 patients, ages 3–25, with a clinical history of AD for more than 2 years and an initial SCORAD over 15. Research in AIT efficacy in HDM-sensitized patients showed similar results with a dose-dependent decline in SCORAD after 1 year of AIT therapy and a decrease in topic corticosteroid use [4]. However, a Cochrane review meta-analysis of 12 eligible trials found there was not enough evidence that AIT is effective in treating AD and that the evidence available was of low quality [51•]. Conversely, a similar meta-analysis conducted by Bae et al. included 8 randomized control trials and found that patients with improvements in their AD symptoms had an odds ratio (OR) of 5.35 of being treated with AIT when compared with placebo. Researchers also calculated the number needed to treat as three [52]. Significant heterogeneity leads this meta-analysis to being given a moderate quality evidence rating as per the Grading of Recommendations Assessment, Development and Evaluation score. Although reaching opposing conclusions, both articles highlighted the need for better studies with larger population sizes and less heterogeneity.

Due to the controversial nature and conflicting evidence on the use of AIT for patients with AD, the current recommendations rely on clinicians' judgment. Recommendations posed by Ridolo et al. revolve around three considerations:

a. Sensitization to aeroallergens must be proven with skin prick test and/or IgE assay
b. Exposure to aeroallergens induces AD flare-ups
c. Physician must choose a standardized product for AIT [53••]

Similarly, Boguniewicz et al. suggest that a trial of AIT can be considered for patients with a positive allergen test and history of AD symptoms being triggered by exposure to that allergen. We must also underline that the evidence for such a course of treatment is limited [54•]. The most recent guidelines from the American Academy of Dermatology suggests that there is insufficient data to recommend AIT use, whereas the Joint Task Force suggest that clinicians can consider AIT use in select patients with aeroallergen sensitivities [55]. The European Academy of Dermatology's recent guideline agree with the Joint Task Force that although AIT should not be

first-line treatment for all AD patients, there is a subset of highly sensitized patients with house dust mite, birch or grass pollen sensitization with symptom exacerbation that may benefit [14].

Conclusion

Given the conflicting evidence as to the efficacy and utility of AIT, it is currently unclear as to whether AIT is a wise therapy alternative for patients with AD. For patients whose disease is refractory to other modalities, AIT should be considered on an individual basis by the clinician and discussed with patients to improve treatment literacy and long-term treatment compliance. In order to facilitate these clinical decisions, we suggest the development of an algorithm-based calculator that would enable clinicians to more accurately assess the utility of AIT use in practice as well as recapitulate the need for higher quality research. Additionally, we recognize the relatively recent approval of several biologics, such as dupilumab for use in AD and recommend that these can be used in conjunction with personalized AIT to find the therapeutic regimen that best fit a particular patient. AD remains to be a widely prevalent disease that can impact patient quality of life and this research can significantly impact patient outcomes.

Compliance with Ethics Guidelines

Conflict of Interest Dr. De Benedetto has served on advisory board for Regeneron & Sanofi and Allakos. She has been an investigator for Novartis, Kiniksa, Alchem, Regeneron and Sanofi. Drs. Rizk and Rodenas declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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