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Is Clinical Tolerance Possible after Allergen Immunotherapy?

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Abstract

There is a growing evidence that allergen immunotherapy (AIT) can provide significant and long-lasting clinical benefit for a number of allergic individuals. However, it is less clear if AIT results in clinical tolerance, which is characterized by a persistent state of clinical non-reactivity to allergens after therapy is finished. Addressing this knowledge gap is particularly relevant for patients undergoing AIT for food allergies, as anything less than complete tolerance could have potentially devastating consequences. An increasing number of studies, in particular those involving oral immunotherapy, are attempting to assess tolerance induction following AIT. Clinical tolerance does appear to be achievable in a subset of patients undergoing AIT, but whether this is equivalent to the type of tolerance observed in nonallergic individuals remains unknown. Developing established criteria for assessing tolerance induction, as well as the use of consistent terminology when describing clinical tolerance, will be important for determining the disease-modifying potential of AIT.

Keywords

Allergen immunotherapy; Tolerance; Sustained unresponsiveness; Desensitization

Introduction

Allergen immunotherapy (AIT) is a potentially disease-altering treatment for atopic disorders. Since its initial description over 100 years ago, AIT remains an important therapeutic option for patients suffering from allergic rhinitis, allergic conjunctivitis,

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allergen-driven asthma, and insect sting allergy [1]. AIT involves giving an allergen to IgE-sensitized individuals in increasing amounts, with the goal of inducing clinical non-responsiveness to the allergen. Subcutaneous immunotherapy (SCIT) has been used extensively for the treatment of allergen-driven respiratory diseases or stinging insect allergy, and its efficacy has been supported by several randomized trials [2–4]. Sublingual immunotherapy (SLIT) has also proven effective for the treatment of allergic rhinitis, primarily in patients allergic to pollens [5]. More recently, the use of oral immunotherapy (OIT) as a treatment for food allergies is being intensely researched [6]. Novel strategies for AIT, including intralymphatic or epicutaneous immunotherapy, are also under current investigation [7]. While AIT is frequently described as a potentially curative treatment for allergic disorders, its ability to induce tolerance to allergens remains understudied. In this report, we will review the evidence for clinical tolerance in patients undergoing AIT.

What is tolerance?

Defining tolerance can be challenging, as the term has different meanings depending upon the scientific or clinical discipline (Table 1). From the perspective of basic immunology, tolerance refers to a state of unresponsiveness of the adaptive immune system to a specific antigen. Immunological tolerance is an active process and involves either deletion, inactivation, or suppression of antigen-specific lymphocytes in central lymphoid organs or peripheral tissues [8]. The development of immunological tolerance is not only important for preventing autoimmunity, but also for averting maladaptive immune responses against innocuous environmental allergens or commensal microorganisms. In the field of clinical allergy, the term tolerance pertains to a lack of clinical reactivity to an allergen. Clinical tolerance implies a state of unresponsiveness that persists regardless of allergen exposure. For example, a person who demonstrates tolerance to peanuts will not develop clinical symptoms upon ingestion, regardless of the frequency or the amount of consumption. This is in contrast to desensitization, which can be defined as a temporary state of clinical non-reactivity that is dependent upon persistent allergen exposure. While clinical tolerance is generally thought to depend upon the establishment of immunological tolerance, the two processes may involve distinct mechanisms. For example, clinical tolerance may rely on modulation of both innate immune cells and lymphocytes [9], whereas the mechanisms of immunological tolerance involve only the adaptive immune system. For this review, we will use the term tolerance to be synonymous with clinical tolerance. As described below, clinical tolerance can develop naturally or be acquired through therapeutic intervention.

In the majority of individuals, clinical tolerance to allergens appears to occur naturally. How natural tolerance to allergens arises is incompletely understood and has been largely inferred from studies of patients undergoing AIT or exposed naturally to high-dose allergen, such as beekeepers and cat owners [10, 11]. Tolerance following high-dose allergen exposure has been suggested to result from the induction of interleukin (IL)-10-producing regulatory T cells (Treg) [12, 13] and the production of inhibitory allergen-specific IgG4 [14, 15]. However, it is possible that tolerance induction by low doses of allergen may involve different mechanisms, such as the extrathymic generation of Treg expressing the transcription factor forkhead box P3 (FOXP3) [16]. Furthermore, the immune pathways leading to tolerance may vary depending upon the site of allergen exposure. For example,

the immuno-suppressive cytokine transforming growth factor beta appears to be essential for tolerance induced at mucosal surfaces but not in the skin [12]. It is also noteworthy that natural tolerance can develop even after allergic sensitization has occurred. This is most evident in children with milk and egg allergies, who will frequently "outgrow" their allergies to these foods [17]. Why allergies naturally resolve in some individuals but not others is unclear, but may involve the induction of allergen-specific Treg and suppression of specific IgE production [18, 19].

When natural tolerance fails to develop, clinical tolerance may be acquired through therapeutic interventions, such as AIT. AIT involves the administration of increasing amounts of allergen, with the goal of reducing allergic symptoms upon natural allergen exposure. AIT can lead to allergen desensitization, which can occur within hours of initiating therapy [20]. However, desensitization is a temporary condition, as clinical responsiveness recurs once AIT is stopped. A more desirable outcome for AIT is induced tolerance, which refers to clinical unresponsiveness to allergens that persists after AIT is discontinued. Induced tolerance following AIT may not be equivalent to natural tolerance, as the mechanisms responsible for these conditions may be distinct. For example, induced tolerance during OIT is characterized by an increase in allergen-specific IgG4, whereas natural tolerance to egg has been associated with low IgG4 levels [21]. Furthermore, natural tolerance is generally thought to be permanent, whereas induced tolerance may wane with time [22]. Because of these differences, the term *sustained unresponsiveness* has been proposed as a more accurate description of the clinical non-reactivity observed after successful AIT in food allergic patients [23••].

Can tolerance be achieved with AIT?

There are a small but increasing number of studies demonstrating that patients may experience long-term clinical benefits after AIT is stopped, although the methodologies and criteria used for determining sustained efficacy are variable. Many studies use the term tolerance to describe the long-term clinical efficacy of AIT. However, the definition of "longterm" appears to vary widely among studies, ranging anywhere from a year to over a decade. Tolerance is also frequently used to describe a reduction in symptomology upon allergen exposure, rather than a complete absence of clinical reactivity. While decreased symptoms may be an adequate outcome of AIT for a person with allergic rhinitis, it is likely unacceptable for someone with food allergies. Overall, the induction of clinical tolerance following AIT likely depends upon multiple factors, including the age of the patient, the length of therapy, the type of allergic disease, the route of allergen delivery, and the allergen itself. Below, we will review the evidence of tolerance induction following AIT for different allergic diseases.

Food Allergy

It is arguable that the induction of clinical tolerance following AIT is most salient for patients with food allergies. A primary goal of food immunotherapy is for patients to consume the food following cessation of treatment. Anything less than complete clinical tolerance would potentially place the patient at risk for serious allergic reactions upon food ingestion. While it is clear that a majority of patients can be desensitized to food allergens

with OIT or SLIT, only a minority appear to develop induced tolerance (sustained unresponsiveness) [8]. The exact definition of sustained unresponsiveness is somewhat arbitrary, but generally refers to a lack of clinical reactivity to the ingested food for 1–6 months following therapy.

Early uncontrolled studies provided hope that food allergic patients could develop clinical tolerance following OIT. In 2007, Buchanan et al. found that two of seven egg-allergic patients undergoing OIT developed clinical tolerance, which was defined as passing a double blind, placebo-controlled food challenge (DBPCFC) 3–4 months after stopping therapy [24]. A few years later, Vickery et al. evaluated tolerance induction in six children (ages 3–13 years) undergoing egg OIT using a conditionally increased dosing strategy based on egg white IgE levels. All six patients passed a DBPCFC 1 month after discontinuing therapy [25]. In 2012, Keet et al. assessed tolerance in milk-allergic subjects receiving either SLIT or OIT, with the OIT cohort further divided into either low- or high-maintenance dosing groups [26]. Only one often subjects receiving SLIT passed a DBPFC 6 weeks after therapy completion, compared to 8/20 in the OIT groups (3/10 in the low-dose group and 5/10 in the high-dose group). However, in a follow-up study of five tolerant subjects from this trial, only three were regularly consuming milk when surveyed roughly 3 years after OIT [27•].

Only a few controlled trials have evaluated tolerance induction following food immunotherapy. In 2007, Staden et al. [28] investigated tolerance in 45 children with egg- or milk-allergy verified by food challenge. Subjects were randomized to either OIT or elimination diet for a median of 21 months. OIT was then discontinued for 2 months, and both groups underwent a DBPCFC. The OIT and elimination groups had similar pass rates (36 and 35 %, respectively), and therefore, it was unclear if tolerance had been induced by OIT or developed naturally. In 2012, a randomized, double-blind, placebo-controlled trial by the Consortium for Food Allergy Research (CoFAR) evaluated desensitization and sustained unresponsiveness in egg-allergic children randomized to either OIT (40 subjects) or placebo (15 subjects) [23••]. After 22 months of therapy, 75 % of the OIT group passed a DBPCFC and were considered desensitized. Conversely, no subjects from the placebo group passed a DBPCFC after 10 months of therapy. After discontinuing therapy for 4–6 weeks, 28 % of the OIT-treatment group passed another DBPCFC at 24 months and were labeled as having sustained unresponsiveness. These patients were instructed to add egg to their diet *ad libitum* and did not report any adverse effects when surveyed 12 months later. A limitation to this study was that no subjects from the placebo group were assessed for tolerance at 24 months, although the likelihood of spontaneous resolution of egg allergy was extremely low for this patient cohort.

In a recent report by Vickery et al. [29•], sustained unresponsiveness was evaluated in a peanut-allergic cohort that had been previously desensitized with peanut OIT [30]. In this pilot study, 24 patients were treated for up to 5 years with peanut OIT at doses up to 4000 mg of OIT/day All 24 patients became desensitized as determined by passing a DBPCFC with 5000 mg of peanut while on therapy. After discontinuing therapy for 4 weeks, 50 % of subjects passed another DBPCFC and were considered tolerant. Over a median follow-up period of 40 months, all but one of the tolerant patients was regularly consuming peanuts

with no adverse effects. Notably, the one tolerant patient who did not incorporate peanut into their diet experienced an increase in peanut-specific IgE and skin test wheal size, suggesting recurrence of their peanut allergy. While this study lacked a placebo-controlled comparison group, it is extremely unlikely that half of the subjects would have naturally developed tolerance during the trial. That same year, Syed et al. [31•] evaluated tolerance induction in a phase I study involving 23 peanut-allergic patients receiving peanut OIT or 20 age-matched controls undergoing standard of care (peanut avoidance). After 24 months, 20 of 23 OIT subjects passed a DBPCFC and were considered desensitized, whereas all control patients failed the challenge. After stopping therapy for 3 months, 7 of 20 patients passed a subsequent DBPCFC and were thus labeled as tolerant. However, when OIT was held for another 3 months (6 months total), only three patients remained clinically tolerant. Interestingly, the authors found that the methylation status of the *FOXP3* gene promoter may predict which patients remain tolerant following OIT.

Some preliminary conclusions can be drawn from these studies. For one, clinical tolerance following OIT does develop, albeit in a minority of patients. About 25–50 % of OIT subjects demonstrate clinical tolerance when assessed within 1–3 months of discontinuing therapy. However, this percentage appears to decrease significantly when tolerance is assessed after longer periods of food allergen avoidance. This suggests that the clinical efficacy of OIT is generally transient, and that regular consumption of the allergen is necessary to maintain OIT-induced tolerance. This is clearly different than what is observed for individuals who are naturally tolerant to foods. It is also likely that the duration, dosage, and administration route of food immunotherapy will impact the likelihood of developing tolerance. The relatively high rate of sustained unresponsiveness observed by Vickery et al. may be related to the long duration of therapy (up to 5 years) and high dose of OIT (4000 mg). The higher doses achieved with OIT might explain its apparent superiority to SLIT for desensitizing patients and inducing sustained unresponsiveness [26, 32]. Finally, nearly all of these studies are limited by the lack of a control group during tolerance assessment. While observational studies would suggest that natural resolution of food allergy would be highly unlikely in the patient cohorts studied, this needs to be more rigorously addressed. In summary, while the few small studies to date are promising, larger placebo-controlled trials are necessary for accurately determining tolerance induction following food immunotherapy.

Allergic Respiratory Disease

There is substantial evidence that SCIT and SLIT are effective in reducing allergic symptoms in patients sensitized with allergic respiratory diseases, such as allergic rhinitis and asthma [3, 5]. A number of older studies have also found some persistent clinical benefits after AIT is stopped, which has been interpreted by some as evidence for tolerance induction. In a small double-blind study, Naclerio et al. evaluated the efficacy of SCIT in ragweed-allergic patients 1 year after therapy cessation [33]. Discontinuation of SCIT did not lead to worsening symptoms, but did result in increased nasal responses upon ragweed challenge. Durham and colleagues studied the long-term effects of grass pollen SCIT in small double-blinded, randomized, placebo-controlled trial [34]. Patients treated with SCIT for 3–4 years were randomized to either continue treatment or receive placebo injections for another 3 years. Discontinuation of AIT did not result in increased symptoms scores or

medication usage over the 3-year period. Patients in the discontinuation group did have a slight increase in allergen sensitivity as determined by skin-prick testing and conjunctival allergen challenge, but their reactivity was still significantly lower than that observed in a control group of patients who had never received AIT. Jacobsen et al. evaluated the long-term clinical benefit of SCIT in 147 children with birch or grass pollen allergy [35]. After 10 years, children who had received 3 years of SCIT had lower rates of asthma when compared to untreated patients (25 vs. 45 %, respectively), although bronchial responsiveness to methacholine did not vary between groups. SCIT patients also had slightly reduced conjunctival sensitivity (relative to baseline) 10 years after therapy.

More recently, Tabar et al. [36] performed a prospective study where patients with house dust mite (HDM) allergy were randomized to either 3 or 5 years of SCIT. At the end of 3 years of therapy, both groups demonstrated similar improvement in asthma and rhinitis symptoms when compared to baseline. At the end of 5 years, overall clinical improvement was similar in the two groups. Two additional years of AIT further improved rhinitis symptoms, but not asthma symptoms or quality of life assessments. While objective measurements of clinical reactivity were not assessed, this study suggests that 3 years of therapy can induce some degree of clinical improvement for at least 2 years.

There have also been an increasing number of studies evaluating the sustained efficacy of SLIT for patients allergic to aeroallergens. In a randomized, double-blind, placebo-controlled trial, Durham et al. [37, 38•] investigated the sustained efficacy of standardized grass pollen SLIT up to 2 years following the completion of 3 years of treatment. Compared to placebo, 3 years of SLIT resulted in a 29 and 40 % reduction in rhinoconjunctivitis symptoms scores and medication use, respectively [37]. Two years after discontinuing SLIT, rhinoconjunctivitis symptom scores remained significantly reduced by 25 % in the treatment group compared to the placebo group [38•]. Medication use was also decreased by 20 % in the treatment group, but this did not reach statistical significance. SLIT patients had sustained increases in serum levels of allergen-specific IgG4 and IgE-blocking factor at 2 years following therapy. This is in contrast to a prior study of SCIT for grass pollen allergy [39], where allergen-specific IgG4 decreased after stopping therapy, suggesting that SCIT and SLIT may affect B cell responses differently.

Didier et al. evaluated the sustained efficacy of a 5-grass pollen sublingual tablet in 435 participants enrolled in a randomized, double-blind, placebo-controlled trial. Treatment with the 5-grass tablet or placebo began either 2 or 4 months prior to the pollen season and was continued throughout the season. After 3 years, both treatment groups had significant improvements in adjusted rhinoconjunctivitis symptom scores when compared to placebo [40]. These improvements were maintained during the post-treatment pollen season, indicating that the treatment effect persisted for at least 1 year after therapy [41].

Recently, the sustained efficacy of SLIT for patients with HDM allergy was assessed in a large randomized, double-blind, placebo-controlled trial [42•]. Five hundred nine subjects were randomized to treatment with 300 index of reactivity (IR) tablets, 500 IR tablets or placebo for 12 months, after which therapy was stopped for 1 year. After 12 months of treatment, both tablets resulted in significant decreases of 18–20 % in average adjusted

symptom scores when compared to placebo. Importantly, these benefits persisted for up to 1 year following therapy cessation. A limitation to these studies was that clinical reactivity was not assessed by pre- and post-treatment allergen challenges. In summary, SLIT for aeroallergen sensitivity appears to result in measurable clinical improvement for 1–2 years after therapy cessation.

Because SCIT and SLIT require treatment for several years before significant efficacy is observed, patient compliance is frequently problematic. Therefore, alternative immunotherapy strategies that expedite tolerance induction are being actively investigated. A recent study involving cat-allergic adults evaluated the efficacy of in-tradermal injections of synthetic peptides derived from the major cat allergen Fel d 1 [43]. The participants were randomized to placebo or one of two dosing regimens given over a 12-week period. Sustained efficacy was assessed in 89 subjects by aeroallergen challenge in an environmental exposure chamber. The authors found that a total of four monthly vaccine injections were sufficient to significantly reduce allergen-induced symptoms for up to 9 months after therapy. Intralymphatic immunotherapy (ILIT) has also been proposed to induce more rapid clinical benefit compared to standard regimens of SCIT. In an open-label trial involving 165 grass pollen-allergic subjects, three intralymphatic allergen injections over 2 months resulted in sustained efficacy for up to 3 years as determined by nasal provocation testing [44]. In a small placebo-controlled trial [45], ILIT with modified Fel d 1 improved nasal tolerance to cat allergen at 5 weeks following therapy; however, the study was not powered to assess long-term benefit. In contrast to these studies, a small randomized control trial evaluating 38 grass-allergic patients found no difference in symptom and medication scores between the ILIT or placebo groups [46]. Thus, the efficacy of this strategy remains to be fully determined.

Stinging Insect Allergy

Similar to food allergy, stinging insect allergy can be associated with severe and potentially fatal systemic reactions upon allergen exposure. Venom-allergic patients with a history of sting-induced anaphylaxis have a 30–60 % chance of developing systemic reactions upon subsequent stings [47]. Subcutaneous venom immunotherapy (VIT) is highly effective in desensitizing venom-allergic patients, as greater than 90 % of patients receiving therapy are protected from sting-induced anaphylaxis in several controlled trials [2]. Few studies have evaluated the long-term efficacy of VIT after discontinuing therapy, but those that have suggest that the great majority of patients remain protected against venominduced anaphylaxis. Golden and colleagues evaluated the incidence of sting-induced systemic reactions in adults who had completed 5 years of VIT [48]. Over a 4-year follow-up period, only 7 of 74 patients developed systemic symptoms when subjected to sting challenges after treatment cessation. A follow-up survey of this cohort found that about 85 % of patients remained protected from sting-induced anaphylaxis for up to 10 years after stopping VIT [49]. Lerch and Muller reported similar findings in a study of 200 patients who had received VIT for at least 3 years [50]. They found that during a period of 1–7 years after stopping therapy, only 12.5 % of patients' experienced systemic reactions upon subsequent stings.

Children receiving VIT also appear to develop long-lasting protection. A survey of patients who received VIT during childhood found that only 5 % developed sting-induced systemic reactions over a 10- to 20-year period after stopping therapy [51]. More recently, Stritzke and Eng reported on the outcomes of 83 children undergoing VIT for a mean duration of 3.6 years [52]. This retrospective study found that 15 % of honey bee allergic and 6 % of Vespula allergic patients developed systemic reactions upon subsequent stings. However, only 11 % of patients were stung while off of VIT, and the study was not powered for determining efficacy after therapy cessation.

Conclusions

There is growing evidence that AIT can result in significant and sustained clinical improvement for a number of patients suffering from allergic disorders. Recently, studies of OIT have suggested that clinical tolerance can be induced in a subset of food allergic patients. However, it is unclear if this state of tolerance is truly independent of regular consumption of the food, and therefore not merely a form of prolonged desensitization. In patients sensitized to aeroallergens, SCIT and SLIT can lead to decreased symptoms for several years after therapy cessation, but more objective evidence of tolerance induction is needed. VIT can provide long-term protection against sting-induced anaphylaxis, but how this sustained benefit relates to clinical tolerance requires more investigation. Overall, it remains to be determined if the clinical tolerance induced by AIT is equivalent to "true" tolerance—that is, a permanent state of clinical non-reactivity equivalent to that experienced by nonallergic individuals. Appropriately addressing this question will require long-term follow-up studies that incorporate objective methods for assessing clinical reactivity upon allergen challenge. Such studies will ultimately provide the necessary evidence for what can, and cannot, be attained with AIT.

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Table 1
Terminology used when describing tolerance

Term	Description
Immunological tolerance	• Unresponsiveness of the adaptive immune system to a specific antigen • Involves deletion, inactivation (anergy) or suppression of antigen-specific lymphocytes
Clinical tolerance	• A state of clinical non-reactivity to an allergen • Generally considered permanent and independent of recurrent allergen exposure • May be present in allergen-sensitized individuals
Natural tolerance	• Clinical tolerance that develops as a result of natural exposure to allergens • May occur as the initial response to an allergen, or develop spontaneously in previously allergic individuals
Induced tolerance (sustained unresponsiveness)	• Clinical tolerance that occurs in allergic subjects as a result of allergen immunotherapy • May involve mechanisms that are distinct from those of natural tolerance • Sustained unresponsiveness is used to describe persistent clinical non-reactivity in food allergy patients after successful immunotherapy
Desensitization	• A temporary state of clinical non-reactivity that is dependent upon continuous exposure to allergen