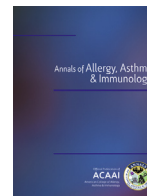




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Specific immunotherapy in the treatment of atopic dermatitis: a systematic review using the GRADE system

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ABSTRACT

Background: Controversy exists regarding the potential role of specific immunotherapy (SIT) as a therapeutic intervention for patients with atopic dermatitis (AD) and aeroallergen sensitivity.

Objective: To critically appraise the evidence supporting the use of SIT for patients with AD and aeroallergen sensitivity.

Methods: A literature search was performed using the terms *immunotherapy* plus *atopic dermatitis* and *immunotherapy* plus *eczema*. The same terms were used to search PubMed, Ovid, and Scopus. The limits were *humans*, *English*, and *randomized controlled trial*. Articles that were not in English or were observational in nature were excluded. These double-blinded randomized controlled trials were analyzed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: Seven articles fulfilled the inclusion characteristics; 1 involved sublingual SIT. All studies reported improvement in clinical symptoms of AD; however, studies differed in which type of patient (ie, with mild vs severe AD) benefited most from immunotherapy. Serious methodologic shortcomings were noted, including, but not limited to, many enrolled patients not completing participation; small study; and incomplete descriptions of randomization, blinding, allocation concealment, and/or data analysis not by intention to treat.

Conclusions: In a systematic review using the GRADE system, the strength of recommendation is weak for use of SIT in patients with AD. High-quality evidence from methodologically sound double-blinded randomized controlled trials is needed to support administration of SIT for patients with AD.

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Introduction

Atopic dermatitis (AD) is a chronic pruritic skin condition often associated with other allergic disorders, such as allergic rhinoconjunctivitis and asthma. The prevalence of AD has increased during the past 3 decades. Approximately 15% to 30% of children and 2% to 10% of adults are affected.¹ The cause of AD is not completely understood, but this condition is associated with an elevated IgE, IgE-bearing Langerhans cells, and the infiltration of T-helper type 2 cells and their associated cytokines. Patients with AD often are sensitized to aeroallergens, and in some patients flares may occur after exposure to dust mites and pollens.² Dust mite control measures have been associated with alleviation of AD symptoms.^{3,4}

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Specific allergen immunotherapy (SIT) has been used for at least a century to desensitize patients to aeroallergens.⁵ Desensitization has been defined as “the rapid administration of incremental doses of allergens or medications by which effector cells are rendered less reactive or nonreactive to an IgE-mediated immune response.”⁶ There have been many high-quality randomized controlled studies showing that SIT is an effective treatment for allergic rhinitis and asthma.⁷ The Allergen Immunotherapy Practice Parameter, 3rd Update (2011) states: “there is also some evidence that patients with AD with aeroallergen sensitivity might benefit from immunotherapy.”⁶ Similarly, the 2012 update of the AD practice parameter states: “On the basis of several studies of dust mite immunotherapy, the clinician might consider allergen immunotherapy in selected patients with AD with aeroallergen sensitivity.”⁸

The efficacy of SIT is thought to entail increasing CD4⁺CD25⁺ regulatory T lymphocytes secreting interleukin-10 and transforming growth factor- β and a switch from a T-helper type 2 to type 1 cytokine response. These changes lead to a decrease in end-organ response during allergen challenges. Because SIT modifies the immune response to aeroallergens in patients with allergic rhinitis and asthma, it might modify the immune response in patients with AD in association with aeroallergen exposure.

Patients whose symptoms are not well controlled on medication and avoidance measures or who prefer to decrease medication reliance for control of symptoms are candidates for SIT. There have been 2 reviews that have examined the efficacy of SIT for AD,^{9,10} but many of the studies described were observational in nature and a systematic approach was not used to critically appraise each study.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is a systematic method for evaluating quality of evidence and formulating a strength of recommendation.¹¹ This approach leads to a recommendation for or against an intervention with a grading of the strength of the recommendation based on whether the potential for benefit outweighs the potential for harm or burden and a consideration of patient values and preferences.¹² The quality of evidence is divided into 4 categories: high, moderate, low, and very low. In the present evaluation of the quality of individual studies, the term *very low* was not used. The GRADE system clearly defines the methodologic criteria by which evidence can be upgraded or downgraded and the justification for the strength of recommendation being formulated as “strong” or “weak.”¹³

A systematic review was carried out to critically appraise the evidence supporting the use of SIT for patients with AD using the GRADE approach.

Methods

A literature search was performed using the terms *immunotherapy plus atopic dermatitis* and *immunotherapy plus eczema*. The same terms were used to search PubMed, Ovid, and Scopus. The limits were *humans*, *English*, and *randomized controlled trial*. Excluded from this review were articles that were not in English or were observational in nature. Also excluded were articles in which the treatment was not SIT, such as interferon- γ therapy or *Mycobacterium tuberculosis* vaccination.

Studies were selected that were randomized controlled trials that met the inclusion and exclusion criteria. Studies were assessed for the description of randomization and blinding in regard to efficacy. Strength of evidence was critically appraised for risk of bias (allocation concealment, incomplete data, and other sources of bias), indirectness, inconsistency, magnitude of effect, analysis by intention to treat, and external validity.

Results

Seven randomized controlled trials were identified that met the inclusion and exclusion criteria (Table 1).^{14–20} Participants in these trials had chronic, severe, poorly controlled, and/or refractory AD and IgE-mediated potential to aeroallergens corroborated by a positive skin prick test result or serum-specific IgE.

Except for 1 study,¹⁴ patients continued skin moisturizing and treatment with topical steroids and oral antihistamines. Patients were randomized to receive placebo or SIT with dust mites and/or other aeroallergens. One study evaluated the dose and response of dust mite subcutaneous immunotherapy (IT), with an active placebo dose of 20 standardized quality units (SQ-U) per week.¹⁵ Five entailed administration of SIT for dust mite alone, 1 used grass pollen, and 1 used a combination of inhalant antigens. Five used subcutaneous IT, 1 used sublingual IT, and 1 used intradermal IT.

The primary outcome in all studies was an objective measurement of AD severity; the 3 more recent studies used Scoring Atopic Dermatitis (SCORAD).^{14,15,20} Secondary outcomes included the visual analog scale, medication use, adverse events, Dermatology Life Quality Index, and laboratory values, such as total IgE, specific IgE, and specific IgG4 levels.

The objective measurement of AD extent and intensity (eg, SCORAD) significantly improved in patients receiving SIT vs placebo

in all studies. In 1 study,¹⁴ the change in SCORAD significantly improved from month 9 in patients with mild to moderate AD (SCORAD <40), whereas there was no significant change in patients with severe AD (SCORAD >40). This is in contrast to the most recent study,²⁰ in which no statistically significant difference was observed between the actively treated and placebo-treated groups overall, but in post hoc subgroup analysis, patients with severe AD (SCORAD >50) showed a statistically significant decrease of the median total SCORAD by 21%. Three other studies also found improvement in patients with severe AD with the use of SIT.^{15,16,18} In another study,¹⁶ the difference in eczema severity between treatment and placebo was not statistically significant after 6 months of injections; by 12 months, there was a significant difference between the 2 groups using the physician-scored severity/body surface area scale, whereas parent assessments of improvement in eczema severity after 12 months of active treatment were 62% for children randomized to the active group and 82% for those randomized to the placebo group.

Five studies recorded adverse effects of SIT. In 1 study,¹⁴ there were 2 patients in whom sublingual IT was discontinued due to worsening of AD. In a study using intradermal antigen–antibody complexes,¹⁸ 8 patients reported a flare in their dermatitis within 48 hours of injection: 6 received placebo and 2 received active treatment. In a study by Novak et al,²⁰ 8% of actively treated patients and 10.7% of placebo-treated patients had systemic adverse reactions of grade 1 or 2, such as flare-ups of eczematous and urticarial lesions. Overall, SIT was found to be very safe and AD worsened in only a small proportion of patients on this treatment.

There was no significant change in total or specific IgE before and after treatment in 3 of 5 studies in which this was assessed. In 1 study,¹⁹ there was a significant decrease in total IgE, but no change in specific IgE before or after treatment. In another study,²⁰ there was a statistically significant decrease in total IgE and specific IgE to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* and an increase in *D pteronyssinus*–specific IgG4.

Four of the 7 studies recorded medication usage.^{14,15,18,20} In the study by Pajno et al,¹⁴ “allowed medications were short courses (3 days) of topical fluticasone propionate and/or oral hydroxyzine on demand for worsening pruritus, itching, edema, or oozing. In the case of cutaneous superinfection, the physician could prescribe a 6-day course of clarithromycin (15 mg/kg/d). No other treatment, including moisturizers, was allowed during the study.” This is unusual in that other studies allowed use of topical moisturizers and oral antihistamines and topical corticosteroids throughout the study. This study and 2 others^{15,20} found a decreased need for topical corticosteroids and systemic antihistamines in the treatment groups. However, in the study by Leroy et al,¹⁸ 4 patients required systemic steroids: 1 placebo vs 3 active.

The 7 randomized controlled trials were evaluated using the GRADE approach. All studies started out as high-quality evidence. One study that included only 2 patients¹⁹ was downgraded based on various limitations (Table 1). Five of the 7 studies did not use an intention-to-treat analysis. Two studies were limited by low power.^{16,19} In another study,²⁰ no description of blinding or placebo was provided. One study administered IT to “study 1” patients for only 6 months,¹⁶ which is unlikely to be an adequate period for the inflammatory changes in AD to improve. There were no studies that included a statement regarding allocation concealment. In 1 study,¹⁵ demographic characteristics were not fully detailed. External validity was limited in 1 study due to using sublingual IT (not available in the United States) and excluding patients who had chronic asthma or food allergy¹⁴ and in another study that entailed administration of autologous specific antibodies and *D pteronyssinus* allergens.¹⁸ Based on these various limitations, 4 studies were downgraded to moderate quality and 3 to low quality.

Table 1

Randomized controlled trials evaluating the use of immunotherapy for the treatment of atopic dermatitis

Reference	Study objective	Patients	Intervention	Standard therapy	Cases enrolled	Completed study, n	Primary outcome	Results	Study limitations ^a	Quality of evidence
Glover and Atherton, ¹⁶ 1992	examine effect of hyposensitization to Dp in childhood AD	5–16 y old with severe AD and positive skin prick reaction to Dp (≥ 4 -mm wheal)	SC injections of Dp; study 1: 6 weekly injections (buildup), then 6 monthly injections; study 2: 6 monthly injections	6-wk pretrial assessment to allow for stabilization of concurrent treatments and avoidance measures	N = 26 (13 active, 13 placebo)	study 1: 13 active, 11 placebo; study 2 (patients taken from active group in study 1, after blinding was revealed): 4 active, 3 placebo	clinical eczema severity (scored 0–3 based on erythema, surface damage, and lichenification) and body surface area affected scored at 8-wk intervals	study 1: no statistically significant difference between treatment and placebo groups; study 2: significant improvement in erythema ($P = .049$) and lichenification ($P = .0415$) in treatment group; no difference in total IgE, specific IgE to Dp, and skin prick responses; more patients randomized to placebo improved in parent assessment compared with treated patients (82% vs 62%, not statistically significant)	some benefit in study 2 but this is difficult to interpret based on low power—only 4 patients received treatment for >8 mo; analysis did not use ITT (risk of bias)	low
Kaufman and Roth, ¹⁷ 1974	evaluate hyposensitization therapy as prime mode of treatment for uncontrolled AD	2–47 y old with AD with ≥ 3 positive inhalant skin test results	SC injections of “tailor-made” inhalant antigens (maximum dose 400 PNU) such as dust mite, animal dander, molds, and pollens; 2-y study	no effort made to control environment or diet; gave general instructions regarding skin hygiene and prescribed topical steroids and antihistamines	N = 56	26 completed 2-y study (16 treatment, 10 placebo)	severity of skin disease scored (improved, no change, or worse) on 24 characteristics ($1-\geq 4$) before and after treatment	significant improvement between treated and placebo: 13/16 (81%) vs 4/10 (40%; $P < .05$)	did not use ITT; excluded 50% of patients initially selected (risk of bias); no environmental control measures or control of patient's diet; no DBFC if positive skin test result to foods	low
Leroy et al, ¹⁸ 1993	determine if ID injections of allergen–antibody complexes improves AD	15–64 y old with severe AD, positive skin prick result, and specific IgE to Dp with total IgE ≥ 20 kU/L	ID injections of autologous specific antibodies and Dp allergens; group A: active treatment from baseline to 12 mo; group B: placebo for 4 mo, then active	6-wk “washout” period: withdrew any medications except antihistamine and topical steroid	N = 24 (12 group A; 12 group B)	N = 23 (12 group A; 11 group B)	DII = mean score of clinical symptoms $\times$ BSA (%); clinical symptoms (erythema, edema, papules, excoriations, lichenification, and desquamation) scored 0–4	significant decrease ($P < .05$) in DII after 4 mo in treated patients only; after 1 y, 82% of patients exhibited a mean improvement of 83%, associated with a decrease of Dp-specific antibodies; VAS	poor external validity due to specific anti-Dp antibodies have to be prepared for each patient	moderate

(continued on next page)

Table 1 (continued)

Reference	Study objective	Patients	Intervention	Standard therapy	Cases enrolled	Completed study, n	Primary outcome	Results	Study limitations ^a	Quality of evidence
Pajno et al, ¹⁴ 2007	assess effect of sublingual IT in children with AD	5–16 y old with AD (SCORAD >7) and sensitization to dust mites alone, without food allergy or chronic asthma	treatment at 4–16 mo sublingual IT with dust mite for 18 mo	oral antihistamine and topical steroid	N = 56 (28 SLIT, 28 placebo)	N = 48 (26 SLIT, 22 placebo)	change in SCORAD from baseline at 3-mo intervals	significantly lower in group A at 4 mo ($P = .008$) and at month 8 for group B ($P = .005$) difference from baseline in SCORAD (10 points) was significant ($P = .025$) starting from month 9; significant decrease in use of medications in treatment group only; in patients with mild to moderate AD (SCORAD <40), change in SCORAD significantly improved from month 9, whereas no change was observed in patients with severe AD; SLIT had to be discontinued in 2 patients because of exacerbation of dermatitis	did not use ITT for efficacy analysis (risk of bias); need increased power for VAS score to show significance; eliminated patients with food allergy or chronic asthma (indirectness); external validity limited for United States	moderate
Ring, ¹⁹ 1982	study effect of hyposensitization treatment in monozygotic twins with AD	10-y-old twins	SC injections with grass pollen extract or saline for 2 y	mild topical corticosteroids, oil baths, emollients, zinc oxide paste	2	2	severity scored (0–4) on 12 skin characteristics (0–48 points) + loss of sleep; extent of BSA using “rule of 9s”	grass pollen extract: treated patient scored 10 points and placebo patient scored 21 points at end of 2 y; dramatic decrease in total IgE in treated patient; no difference in specific IgE	patients in each group = 1 (imprecision)	low
Werfel et al, ¹⁵ 2006	hypothesis: 1 y of SIT would improve AD in dose-dependent manner with Dp/Df allergens	18–55 y old with chronic AD and sensitized against Dp/Df (CAP FEIA ≥ 3 , SCORAD ≥ 40)	SC injections with Dp/Df applying maintenance doses of 20, 2,000, or 20,000 SQ-U weekly for 12 mo	emollients, topical corticosteroids up to class 3, cetirizine and loratadine	N = 89 (28 in 20 SQ-U, 28 in 2,000 SQ-U, 28 in 20,000 SQ-U)	79 in efficacy analogs: 26 in 20 SQ-U, 26 in 2,000 SQ-U, 27 in 20,000 SQ-U; 51 completed 1-y trial	mean difference between average of SCORAD values after 9 and 12 mo of SIT and baseline	SCORAD decreased in all 3 groups; difference in mean SCORAD between groups 3 and 1 was significant ($P = .04$), but not	large number of patients (43%) discontinued SIT: 7/14 in 20 SQ-U group due to efficacy; in 2,000 and 20,000 SQ-U groups due to	moderate

Novak et al, ²⁰ 2012	investigate efficacy and safety of IT using depigmented polymerized mite extract for 18 mo	18–66 y old with moderate to severe AD, aggravated by exposure to HDM during “heating season” (September–February), positive skin prick result to Dp and Df, specific IgE to Dp or Df in a RAST class ≥ 3	SC injections using depigmented polymerized mite extract for 18 mo	topical and systemic medications, encasement of bedding and mattresses for ≥ 6 mo	N = 168 (112 active, 56 placebo); severe AD subgroup: N = 80 (52 active, 28 placebo)	N = 113 (75 active, 38 placebo); severe AD subgroup: N = 52 (36 active, 16 placebo)	total SCORAD and use of basic medications over 18-mo period	between groups 2 and 1 ($P = .13$); need for topical steroids ($P < .001$) and antihistamines ($P = .06$) decreased in groups 2 and 3; no significant change in any group in specific and total IgE or in ECP levels	noncompliance (risk of bias); single blinded with respect to safety; DB with respect to efficacy; did not use ITT (risk of bias); demographic characteristics not fully detailed (indirectness)	moderate
								no significant difference in any parameter between active and placebo groups in primary analysis; in post hoc subgroup analyses, there was a statistically significant decrease in median total SCORAD by 21% compared with placebo in ITT analysis, but this was not statistically significant in PP analysis; medication scores were lower but not significantly different in SCORAD >50 subgroup vs placebo; significant decrease in total IgE, specific IgE to Dp/Df; and increase in Dp-specific IgG4 in overall ITT group; no differences in adverse events between groups	no description of blinding or placebo used (risk of bias)	

Abbreviations: AD, atopic dermatitis; BSA, body surface area; CAP FEIA, fluorescent enzyme immunoassay; DB, double blinded; DBFC, double-blinded food challenge; Df, *Dermatophagoides farinae*; DII, Disease Intensity Index; Dp, *Dermatophagoides pteronyssinus*; ECP, eosinophil cationic protein; HDM, house dust mite; ID, intradermal; IT, immunotherapy; ITT, intention-to-treat analysis; PNU, protein nitrogen units; PP, per protocol; RAST, radioallergo-sorbent test; SC, subcutaneous; SCORAD, Scoring Atopic Dermatitis; SIT, specific immunotherapy; SLIT, sublingual immunotherapy; SQ-U, standardized quality units; VAS, visual analog scale.

^aNone of the studies included a statement regarding allocation concealment.

Discussion

Seven double-blinded randomized controlled trials evaluating the efficacy of SIT for treatment of AD met the inclusion and exclusion criteria in this systematic review and were analyzed using the GRADE approach. Five studies administered dust mite antigen alone, 1 study administered a combination of inhalant antigens, and 1 study administered grass pollen antigen alone. Five of the 7 studies used subcutaneous IT, 1 used sublingual IT,¹⁴ and 1 used intradermal IT¹⁸ with allergen–antibody complexes.

Serious methodologic shortcomings were noted in all studies; for this reason, these studies were downgraded to moderate quality of evidence in 4 cases and to low quality in 3. All studies reported improvement in AD; however, several studies had a large attrition rate and 3 studies reported substantial benefit in patients randomized to placebo. This might be due to study patients having closer follow-up with a specialist, which may improve compliance and adherence to therapy.

Bussman et al⁹ identified 23 studies from 1974 through 2006: 2 case reports, 10 observational studies, and 11 controlled studies. When 5 of the comparable controlled studies were evaluated, statistical analysis showed a significant improvement of symptoms in patients with AD treated with SIT. Seven comparable observational studies showed a mean improvement of 70.8% in patients with AD receiving SIT.⁹ The main weakness of these previous studies is that they were not controlled, had low power, or had a high dropout rate. A more recent review by Compalati et al¹⁰ aimed to assess the quality of evidence for use of SIT in AD published since the review by Bussman et al. Four controlled trials were identified; 1 is included in the present review,¹⁴ 2 were observational, and 1 was in Chinese. The present review was limited to studies that were randomized controlled trials to eliminate lower-quality observational studies.

The primary outcome in all studies was an objective measurement of AD severity and/or extent. However, not all studies used a validated scoring system. The SCORAD was designed in 1993 because of the lack of a standardized assessment method for AD in clinical practice and to develop a composite severity index for statistical analysis in therapeutic trials.²¹ SCORAD takes into account extent (rule of 9s is applied for a score of 0 to 100), intensity (erythema, edema/papulation, excoriations, lichenification, oozing/crusting, and dryness scored; each item scored from 0 to 3), and subjective symptoms (pruritus and sleeplessness graded on a 10-cm visual analog scale scored from 0 to 20). The objective SCORAD eliminates the subjective component and consists only of the extent and intensity items. The intra- and interobserver variations are estimated to be approximately 20% in the objective SCORAD and is one of the most frequently used published scoring systems.²²

Three of the studies in the present series used SCORAD.^{14,15,20} The minimal clinically important differences are 8.7 points for the SCORAD and 8.2 points for the objective SCORAD.²³ In the study by Werfel et al,¹⁵ changes in SCORAD from baseline were –10.0 for the 20 SQ-U group, –16.9 for the 2,000 SQ-U group, and –19.0 for the 20,000 SQ-U group. In the study by Pajno et al,¹⁴ the change from baseline in SCORAD was –12 points by 9 months of treatment, but did not significantly change in the placebo group. In these 2 studies, the change in SCORAD from baseline was greater than the minimal clinically important difference of 8.7 points, implying that a clinically meaningful difference was observed in association with SIT for AD. Figure 2 in the study by Novak et al²⁰ shows a decrease in SCORAD of about 20 points.

Four studies found that patients with severe AD benefited from SIT,^{15,16,18,20} whereas the study by Pajno et al,¹⁴ found no benefit in patients with severe AD (SCORAD >40). It should be noted that the statistically significant findings by Novak et al²⁰ in patients with

severe AD were found in a post hoc analysis, in a study in which the primary outcome analysis between actively and placebo-treated patients was not statistically significant. For this reason, this finding merits confirmation in additional studies.²⁴

Some favorable outcomes have been associated with SIT for allergic rhinitis, including the potential for long-term improvement and prevention of asthma^{25–27} and further inhalant sensitization from developing,^{28–30} by changing the humoral and cellular immune responses to antigens.³¹ Five of the 7 studies in the present series evaluated immunologic changes in patients receiving SIT. In the studies that evaluated the change in total and specific IgE, there was no significant change in total or specific IgE before and after treatment in 3 of the 5 studies. In 1 study,¹⁹ there was a significant decrease in total IgE, but no change in specific IgE before and after treatment. In another study,²⁰ there was a statistically significant decrease in total IgE and specific IgE to *D pteronyssinus* and *D farinae* and an increase in *D pteronyssinus*–specific IgG4.

Another factor to consider while weighing the risks and benefits of IT for patients with AD is the documented increased skin and nasal carriage rate of *Staphylococcus aureus* in patients receiving injections. This phenomenon has been shown in intravenous drug users,³² insulin-injecting patients with diabetes,³³ and patients receiving allergy injections.³⁴ The density of *S aureus* skin colonization has been positively correlated with the severity of AD³⁵ and might act as a superantigen. Therefore, increased skin and nasal *S aureus* carriage in patients with AD receiving IT injections regularly theoretically could lead to worsening in AD.

The burdens of allergen IT were considered in determining strength of recommendation for use of SIT for AD. These included the time to travel to and from a medical treatment center to receive subcutaneous IT and a 30-minute wait period after receiving subcutaneous IT, the pain and anxiety of receiving an injection, the possible anxiety in having an adverse reaction from allergen IT, and the costs of IT vs the cost of oral antihistamines and topical corticosteroids.

Limitations of this study include the exclusion of studies that were not randomized controlled trials and studies not in English. Studies that were not randomized controlled trials were excluded a priori owing to inherent biases in observational uncontrolled studies.

Although the studies included in this systematic review showed an overall improvement in AD in association with SIT and decreased use of medications, the magnitude of improvement was sometimes overshadowed by a large placebo effect, which makes the true effect of SIT in treating AD more difficult to determine. An intention-to-treat analysis was not used in most of these studies, implying that patients who were randomized but did not complete participation were not included in the analysis. It is possible that most patients who dropped out did so because they did not have any improvement in AD symptoms, and therefore excluding them might bias an analysis toward a positive result.

There were methodologic differences in the randomized controlled trials that were identified. In addition to variation in interventions used, in several studies, 50% or more of patients with AD had concomitant asthma,^{16–18} whereas in other studies patients with persistent¹⁴ or more severe^{15,20} asthma were excluded. Two studies enrolled children 5 to 16 years old^{14,16}; other studies enrolled adults,^{15,20} children and adults,¹⁷ or adolescents and adults.¹⁸ Heterogeneity found in a systematic review may be related to differences in populations of patients enrolled, differences in the interventions used, or differences in study duration; however, the available data do not permit an interpretation as to the reason for some of the inconsistencies that were found. Such inconsistency is also a basis for downgrading the level of evidence in support of SIT for patients with AD.³⁶

For patients with AD who have aeroallergen sensitivity, 2 recently published practice parameters recommend SIT, stating, respectively that such patients “might benefit” from SIT⁶ and that the clinician “might consider” SIT.⁸ The present systematic appraisal leads to a weak recommendation for the use of SIT for AD. A weak recommendation is used when there is low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.¹³ The studies in this review were graded as moderate or low quality; this is an area in which further research is likely (in moderate-quality studies) or very likely (in low-quality studies) to have an important impact on the confidence in the estimate of effect and may be likely to change the estimate.

This weak recommendation implies that the decision to prescribe SIT for a patient with AD should be approached carefully from an individualized standpoint in consideration of the potential for benefit compared with the potential for harm and burden, allowing patients to express their values and preferences and participate in the medical decision-making process. High-quality evidence from methodologically sound double-blinded randomized controlled trials is needed to provide further support for administration of SIT for patients with AD.

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