

Efficacy of allergen-specific immunotherapy for atopic dermatitis: A systematic review and meta-analysis of randomized controlled trials

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Background: Allergen-specific immunotherapy (allergen-SIT) is the only treatment directed at the cause of IgE-mediated allergic diseases. However, there is controversy over the use of SIT for patients with atopic dermatitis.

Objective: We performed a systematic review and meta-analysis to assess the efficacy of SIT for patients with atopic dermatitis.

Methods: We performed manual searches of reference lists and computerized searches of the MEDLINE, EMBASE, CINAHL, Web of Science, and Cochrane databases (through December 10, 2012) for randomized controlled trials that compared SIT with placebo for patients with atopic dermatitis. The outcome of interest was a dichotomous variable, in terms of treatment success; a meta-analysis was performed by using a random-effects analysis. Subgroup analyses were carried out to evaluate the effects of long-term treatment (more than 1 year), SIT for severe atopic dermatitis, SIT for children, and subcutaneous and sublingual administration of immunotherapy.

Results: We analyzed 8 randomized controlled trials that comprised a total of 385 subjects. We found that SIT has a significant positive effect on atopic dermatitis (odds ratio [OR], 5.35; 95% CI, 1.61-17.77; number needed to treat, 3; 95% CI, 2-9). SIT also showed significant efficacy in long-term treatment (OR, 6.42; 95% CI, 1.50-27.52) for patients with severe atopic dermatitis (OR, 3.13; 95% CI, 1.31-7.48), and when administered subcutaneously (OR, 4.27; 95% CI, 1.36-13.39).

Conclusions: A meta-analysis provides moderate-level evidence for the efficacy of SIT against atopic dermatitis. However, these findings are based on an analysis of a small number of randomized controlled trials, with considerable heterogeneity among trials. (*J Allergy Clin Immunol* 2013;■■■:■■■-■■■.)

Key words: Allergen-specific immunotherapy, atopic dermatitis, meta-analysis, subcutaneous immunotherapy, sublingual immunotherapy, systematic review

Abbreviations used

OR: Odds ratio
RCT: Randomized controlled trial
SCIT: Subcutaneous immunotherapy
SIT: Specific immunotherapy
SLIT: Sublingual immunotherapy

Atopic dermatitis is a common chronic inflammatory disorder of the skin that affects up to 20% of children and 1% to 3% of adults in industrial countries.¹ It is the product of complex interactions among several genetic factors, deficiencies in skin barrier function, exposure to various allergens and infectious agents, and features of the immune response.² Pathogenesis is believed to involve impairments in the skin barrier followed by a high number of allergen sensitizations via transepidermal penetration.³

Exposure to allergens causes repetitive flares of atopic dermatitis in some patients. Most patients are frequently observed to have increased serum levels of total IgE and allergen-specific IgE, and up to 50% of the patients have positive results from an atopy patch test.⁴ Allergens on the skin are believed to be internalized by IgE receptor-bearing epidermal dendritic cells, which initiate the inflammatory process.⁵ The most common allergens that elicit eczema are derived from house-dust mites of the species *Dermaphagoides pteronyssinus* and *D farinae*; avoidance of these mites can benefit patients with atopic dermatitis.⁶

Allergen-specific immunotherapy (allergen-SIT) was first described by Noon in 1911,⁷ and remains the only treatment directed at the cause of IgE-mediated allergic diseases. The basic principle of SIT is to induce immune tolerance to allergens by administering them to patients in repeated, increasing doses.⁸ SIT can be administered subcutaneously (called subcutaneous immunotherapy [SCIT]) and sublingually (called sublingual immunotherapy [SLIT]). SCIT is effective for patients with allergic rhinitis,⁹ bronchial asthma,¹⁰ and venom anaphylaxis.¹¹ SLIT has emerged as an effective alternative to SCIT and is widely practiced for patients with allergic rhinitis in Europe.¹²

Contradictory clinical observations and differences in models of the immune response have led to controversy over the efficacy of SIT for patients with atopic dermatitis.^{13,14} Although several comprehensive systematic reviews have shown that SIT could improve the course of atopic dermatitis, many of the studies included were uncontrolled or not randomized, or were observational, and therefore had the potential for bias.¹³⁻¹⁷ Furthermore, the effects of SIT for patients with atopic dermatitis have never been quantitatively estimated, because of the small number of randomized controlled trials (RCTs), with significant heterogeneity in design.

Nonetheless, evidence is needed regarding the efficacy of SIT for atopic dermatitis. We therefore performed a meta-analysis of

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data from published RCTs by using a statistical method that combines different types of outcomes such as dichotomous and continuous variables.¹⁸

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁹

Search strategy

Two researchers (J.M.B. and Y.Y.C.) performed independent, comprehensive searches of the following databases, from inception through December 10, 2012: MEDLINE (accessed by PubMed), EMBASE, CINAHL, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library. By using a highly sensitive search strategy to identify RCTs,²⁰ we searched for the following terms: “atop*,” “dermatitis,” “eczema,” “allergen-specific immunotherapy,” “immunotherapy,” “immune therapy,” “hypo-sensitization,” and “desensitization.” The search was limited to human studies but not restricted to any particular language or publication date. Reference lists from all available review articles and RCTs were also searched manually.

Study selection

The review included RCTs of children or adults diagnosed with atopic dermatitis who were randomly assigned to at least 2 groups that received SIT (treatment) or placebo (control), with at least 5 participants in each group (irrespective of dropouts). The review did not include any duplicate publications or substudies, or studies in which the control group received anything beyond conventional treatment (topical steroids, oral antihistamines, or short-term systemic steroids). The review included trials in which participants were allowed to receive short-term therapy with systemic steroids, because it is difficult to control atopic dermatitis without any flares until immune tolerance is achieved. Short-term systemic administration of steroids might not affect induction of long-term changes to the immune response by SIT. To avoid double counting of patients included in more than 1 article by the same authors or research groups, patient recruitment periods were evaluated, and if necessary, authors were contacted for clarification.

Titles and abstracts of retrieved articles were independently evaluated by 2 researchers (J.M.B. and Y.Y.C.). Full-text articles were reviewed when abstracts did not provide sufficient information about inclusion and exclusion criteria. We independently evaluated the full text of each article and determined eligibility for inclusion in the review. Results were compared and discrepancies resolved through discussion and, if necessary, inclusion of the third researcher (C.O.P.).

Assessment of the risk of bias

Two researchers (J.M.B. and Y.Y.C.) independently assessed the risk of bias of each trial by using the Cochrane Collaboration's Risk of Bias tool.²¹ We assessed the risk of bias during random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, analysis of incomplete outcome data, selective reporting, and in other areas. All these judgments were categorized as “yes” (low risk of bias) or “unclear” or “no” (high risk of bias).²¹

Primary outcomes

In trials of SIT in patients with atopic dermatitis, clinical efficacy was measured by different methods. The primary outcome of interest was dichotomized in terms of treatment success, defined as the proportion of patients whose condition improved, as assessed by the investigators or patients, regardless of different evaluation methods. We also included outcomes of continuous variables, measured by any scoring system, to estimate the percentage reduction from baseline in the SIT and control groups. The studies' primary authors were contacted for further information when needed.

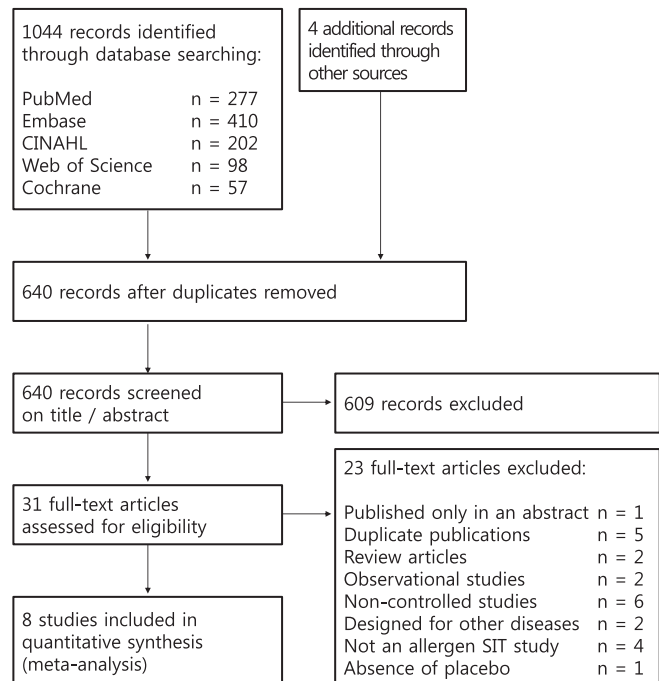


FIG 1. Flow diagram for selecting studies.

Adverse events

Adverse events to immunotherapy were classified as local (local discomfort, redness, or wheal reaction at injection site) or systemic (anaphylaxis, asthma, or urticaria). Events of transient exacerbation of atopic dermatitis were also evaluated. These are summarized qualitatively in the Results section.

Data extraction

Each of the suitable reports was read in detail by J.M.B., Y.Y.C., and C.O.P., and relevant details were summarized in standard extraction sheets (study type and methodology; numbers and descriptions of subjects; details of drug type, dosage, schedule, and period of interventions; outcome types, timing, and measurement methods; local or systemic adverse events; and transient exacerbation of atopic dermatitis). An intention-to-treat analysis was planned, and we attempted to include dropouts in the analysis of dichotomous variables. For continuous variables, we used the last observation carried forward method, if possible. If not, we included patients with a final assessment in the analysis. For studies that presented data in only graphs, the graphs were digitized and values were obtained by using Plot Digitizer Version 2.5.1 (<http://plotdigitizer.sourceforge.net/>).

Data synthesis

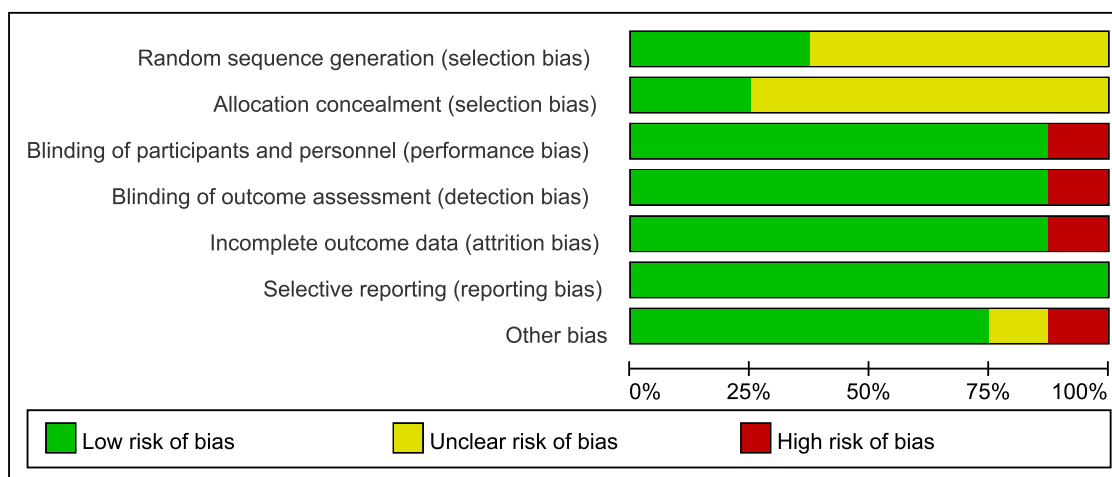
We calculated odds ratios (ORs) with 95% CIs for studies with dichotomous outcomes. For studies with continuous variables, we calculated the standardized mean difference and 95% CIs, and then transformed the standardized mean difference into ORs, so that we could combine outcomes of dichotomous and continuous variables. Standardized mean difference can be re-expressed as log OR by multiplying by $\pi/\sqrt{3} = 1.814$, based on the assumption that the continuous measurements from each group followed a logistic distribution, and the variability of the outcomes was the same for SIT and control groups.¹⁸ We performed a meta-analysis of ORs by using the generic inverse variance method with a random-effects model.²² The number needed to treat was calculated from the results of a meta-analysis of ORs, to aid interpretation.

Heterogeneity among studies was analyzed by using the χ^2 test; a *P* value of less than .1 indicated significant heterogeneity. To further assess heterogeneity, we used the *I*² statistic, which calculates the percentage of total variation among trials because of heterogeneity rather than sampling error. *Post hoc* sensitivity analysis was conducted to examine whether the overall finding was robust to

TABLE I. Characteristics of trials included in the review

Study, year	Country	Study design	Diagnosis criteria	Participants (age range, y)	Intervention			Outcomes
					Type	Allergens	Duration (mo)	
Kaufman and Roth, ²⁴ 1974	US	qRCT DB PC	Confirmed by a dermatologist	52 Children and adults (2-47) uncontrolled AD (+) prick test	SCIT	D, HDM, molds, P	24	Treatment success assessed by physician
Warner et al, ²⁵ 1978	England	RCT DB PC	ND	20 Children (5-14) asthma and AD (+) prick test to DPT	SCIT	HDM	12	Treatment success assessed by patient
Glover and Atherton, ²⁶ 1992	England	RCT DB PC	ND	24 Children (5-16) uncontrolled severe AD (+) prick test to DPT	SCIT	HDM	8	Treatment success assessed by patient
Leroy et al, ²⁷ 1993	Belgium	RCT DB PC	Hanifin and Rajka	23 Children and adults (15-64) severe AD (+) prick test to DPT	SCIT	HDM	4	Disease intensity index assessed by physician
Galli et al, ²⁸ 1994	Italy	RCT PC	Hanifin and Rajka	34 Children (0.5-12) (+) prick test, RAST to DPT	SLIT	HDM	36	Treatment success assessed by physician
Silny and Czarnecka-Operacz, ²⁹ 2006	Poland	RCT DB PC	ND	20 Children and adults (5-40) (+) sensitization to HDM	SCIT	D, HDM, P	12	Treatment success assessed by physician
Pajno et al, ³⁰ 2007	Italy	RCT DB PC	ND	56 Children (5-16) (+) prick test, RAST to HDM	SLIT	HDM	18	SCORAD assessed by physician
Novak et al, ³¹ 2012	Germany	RCT DB PC	Hanifin and Rajka	168 Adults (18-66) moderate to severe AD subgroup analysis of severe AD (+) prick test, RAST to HDM	SCIT	HDM	18	The area under the curve (AUC) values for both SCORAD and the use of basic medication

AD, Atopic dermatitis; D, animal dander; DB, double-blind; DPT, *Dermatophagoides pteronyssinus*; HDM, house-dust mite; ND, not determined; P, pollen; PC, placebo-controlled; RAST, Radioallergosorbent test; qRCT, quasi-randomized controlled trial; SCORAD, SCORING Atopic Dermatitis.

**FIG 2.** Risk-of-bias graph. Our judgment about each risk-of-bias item presented as percentages among all included studies.

1 or 2 outlying studies. In sensitivity analysis, sequential meta-analyses were repeated in which each study was excluded. Subgroup analyses were also carried out to determine the effects of long-term treatment with SIT (more than 1 year), SIT for patients with severe atopic dermatitis, SIT for children, SCIT, and SLIT.

A funnel plot was constructed by plotting the inverse of the standard error against the log OR. The funnel plot summary approach was used to assess publication bias qualitatively. Analysis was performed by using Review Manager, Version 5.1.7 (Nordic Cochrane Center, Copenhagen, Denmark).

Assessing the quality of evidence

We assessed the overall quality of the evidence for our primary outcome by using an adapted Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.²³ The quality of the evidence for a specific outcome was based on performance against the limitations of the study design, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias among all studies that measured that particular

outcome. The overall quality of the evidence for outcome was produced by combining assessments from all domains.

RESULTS

Search results

Of 640 records initially identified (after removing duplicates), the full texts of 31 studies were assessed for eligibility (Fig 1). Twenty-three studies were excluded because they published only an abstract ($n = 1$), were duplicates of other publications ($n = 5$), were review articles ($n = 2$), were observational studies ($n = 2$), were not RCTs ($n = 6$), did not include subjects with atopic dermatitis ($n = 2$), did not test allergen-SIT ($n = 4$), or the control group was not given a placebo or given more than conventional therapy ($n = 1$). After exclusions, 8 RCTs of 385 total patients were available for analysis.²⁴⁻³¹

Description of included studies

All included studies were placebo-controlled RCTs, including 1 quasi-RCT (Table I).²⁴ Two studies were conducted in England,^{25,26} 2 in Italy,^{28,30} and the remaining in the United States,²⁴ Belgium,²⁷ Poland,²⁹ and Germany.³¹ In 3 studies, atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka^{27,28,31}; in 1 study, the diagnosis was confirmed by a board-certified dermatologist²⁴; and in the remaining 4 studies, the diagnostic criteria were not specified.^{25,26,29,30}

Three studies enrolled patients with severe atopic dermatitis that was unresponsive to conventional treatment,^{24,26,27} whereas the other 5 did not specify disease severity. Two studies conducted a subgroup analysis of patients with severe atopic dermatitis.^{30,31} Four studies targeted only children,^{25,26,28,30} 1 targeted only adults,³¹ and 3 had no age limits.^{24,27,29} Six studies tested the effects of SCIT,^{24-27,29,31} and 2 tested the effects of SLIT.^{28,30} Six studies assessed long-term courses of treatment (more than 1 year)^{24,25,28-31}; the remaining 2 studies had treatment periods of 8 months²⁶ and 4 months,²⁷ respectively. The outcome was reported as a dichotomous variable in terms of treatment success in 5 studies^{24-26,28,29} and as a continuous variable in 3 studies.^{27,30,31} In 1 study, the primary analysis variable was the area under the curve values for the total SCORing Atopic Dermatitis (SCORAD) index over an 18-month period, and so we obtained values for analysis from the study's authors.³¹

Risk of bias in included studies

All the included studies were described as randomized. However, few gave specific details of either the method of randomization or concealment of allocation. Blinding of study subjects and investigators was considered adequate in all but 1 study. The results are summarized in the "risk of bias" graph (Fig 2). Fig 3 presents the summary of each risk-of-bias item for each included study.

Effect of interventions

A total of 219 patients were included in the SIT groups and 166 patients in the control groups. A random-effects model pooling of the results showed that SIT had a significantly positive effect on atopic dermatitis (for all 8 studies, OR, 5.35; 95% CI, 1.61-17.77; number needed to treat, 3; 95% CI, 2-9) (Fig 4). Visual inspection of the forest plot and statistical test demonstrated considerable heterogeneity among studies ($P < .05$; $I^2 = 83\%$). Sensitivity analysis (each study sequentially excluded) revealed that the result was robust and not dependent on any individual study (Table II).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Galli et al.	?	?	+	+	+	+	+
Glover et al.	?	?	+	+	+	+	+
Kaufman et al.	?	?	+	+	+	+	+
Leroy et al.	?	?	+	+	+	+	+
Novak et al.	+	+	+	+	+	+	+
Pajno et al.	+	+	+	+	+	+	+
Silny et al.	?	?	+	+	+	+	?
Warner et al.	+	?	+	+	+	+	+

FIG 3. Risk-of-bias summary. Our judgment about each risk-of-bias item for each included study.

Subgroup analysis of the 6 studies of long-term treatment showed significant efficacy for SIT (OR, 6.42; 95% CI, 1.50-27.52) (Fig 5, A). Subgroup analysis of the 5 studies of patients with severe atopic dermatitis also showed significant efficacy for SIT (OR, 3.13; 95% CI, 1.31-7.48) and less heterogeneity in results ($I^2 = 52\%$) than the analysis of all studies (Fig 5, B). However, SIT was not proven to have a significant effect for children in this review (OR, 4.59; 95% CI, 0.49-42.74) (Fig 5, C). SCIT showed a significant effect (OR, 4.27; 95% CI, 1.36-13.39), whereas SLIT did not (OR, 8.18; 95% CI, 0.15-444.38) (Fig 5, D and E). These subgroup analyses did not provide sources of heterogeneity for the overall analysis ($I^2 = 88\%$, 72%, and 94%, respectively). Possible asymmetry was found in the Funnel plots. However, it was difficult to determine the publication bias of outcomes, due to the small number of included studies (graph not shown).

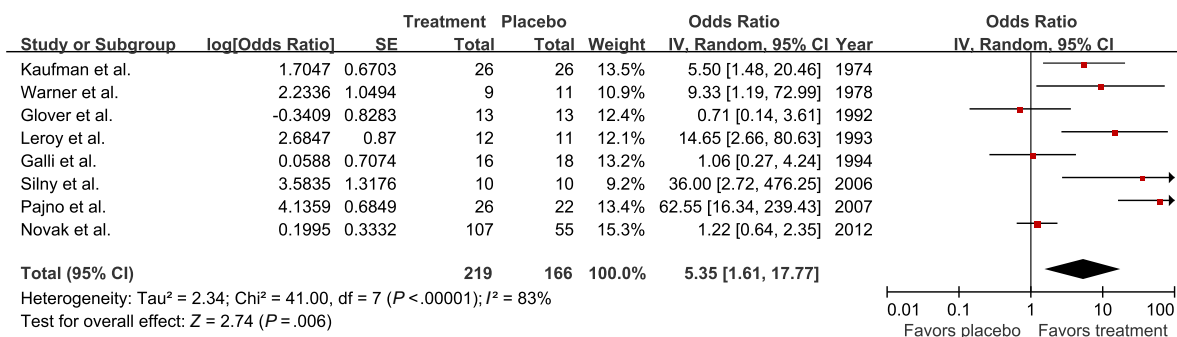


FIG 4. Meta-analysis of 8 RCTs of patients with atopic dermatitis allergen-SIT vs control. A random-effects model was used to produce data.

TABLE II. *Post hoc* sensitivity analysis (each study excluded)

Excluded study	Subjects (n)	I ² (%)	OR	95% CI	P value
Kaufman and Roth, ²⁴ 1974	333	85	5.42	1.34-21.90	.02
Warner et al, ²⁵ 1978	365	85	5.03	1.36-18.62	.02
Glover and Atherton, ²⁶ 1992	359	84	7.16	1.93-26.60	.003
Leroy et al, ²⁷ 1993	362	84	4.67	1.27-17.14	.02
Galli et al, ²⁸ 1994	351	84	6.91	1.78-26.90	.005
Silny and Czarnecka-Operacz, ²⁹ 2006	365	84	4.41	1.27-15.28	.02
Pajno et al, ³⁰ 2007	337	68	3.34	1.26-8.84	.02
Novak et al, ³¹ 2012	223	78	7.00	1.87-26.18	.004
Overall effect	385	83	5.35	1.61-17.77	.006

Adverse events

Adverse events were reported in 7 studies^{24,26-31} and were classified as local or systemic reactions. SIT and control groups had comparable proportions of systemic (0%-8.0% vs 0%-10.7%, respectively) and local reactions (6.3%-80.0% vs 0%-60.0%, respectively). No fatal or near-fatal adverse events were reported in any of the studies assessed. Transient exacerbation of atopic dermatitis was common among patients in SIT groups (14.3%-74%) and control groups (0%-83.3%). However, adverse events have not been clearly defined, and the incidence of reported adverse effects varied among studies, and so it would be a challenge to combine these data from all studies. Table III provides an overview of the adverse events reported.

Quality of evidence

This meta-analysis was rated as providing moderate-quality evidence to support the use of SIT for atopic dermatitis, based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) profile (Table IV). It was initially rated as producing high-quality evidence, because of its inclusion of only RCTs, but unexplained heterogeneity lowered the quality of evidence to a moderate level.

DISCUSSION

Allergen-SIT is the only long-term treatment option directed toward the causes of IgE-mediated allergic diseases.³² The use of allergen-SIT in patients with atopic dermatitis is controversial. Although the efficacy of SIT for atopic dermatitis has been shown

in a number of small controlled and uncontrolled studies, there have been contradictory results.

We performed a comprehensive systematic review and meta-analysis of the efficacy of SIT in patients with atopic dermatitis. This study met most of the methodologic criteria proposed for systematic reviews.¹⁹ A comprehensive search of the published literature for potentially relevant studies was conducted by using a systematic strategy to avoid bias. We did not impose restrictions by language or year of publication, and the search results were complemented by manual searches of relevant journals. The 8 trials included in the final analysis were randomized and mostly double blind; 219 patients received SIT, and 166 received placebo with conventional therapy. Meta-analysis demonstrated the efficacy of SIT, compared with placebo, for patients with atopic dermatitis (OR, 5.35; 95% CI, 1.61-17.77); these findings are supported by the highest ranking in evidence-based medicine. SIT of 3 subjects with atopic dermatitis is necessary for 1 subject to improve (number needed to treat, 3; 95% CI, 2-9).

However, we observed a significant level of heterogeneity among the included studies. Considerable variations among treatment protocols in types and doses of allergens, treatment schedules and durations, and pharmaceutical preparations were assumed to be potential sources of heterogeneity. We had difficulties determining doses and standardizing them among studies, which also used allergen extracts from different sources. However, sensitivity analysis (sequential exclusion of 1 study at a time) indicated the consistent efficacy of SIT, despite the high level of heterogeneity in results.

Subgroup analyses of long-term treatment (more than 1 year), SIT for severe atopic dermatitis, and SCIT also showed significant

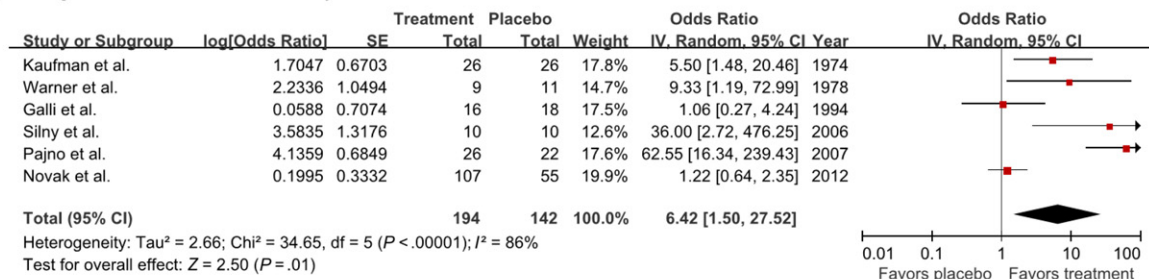
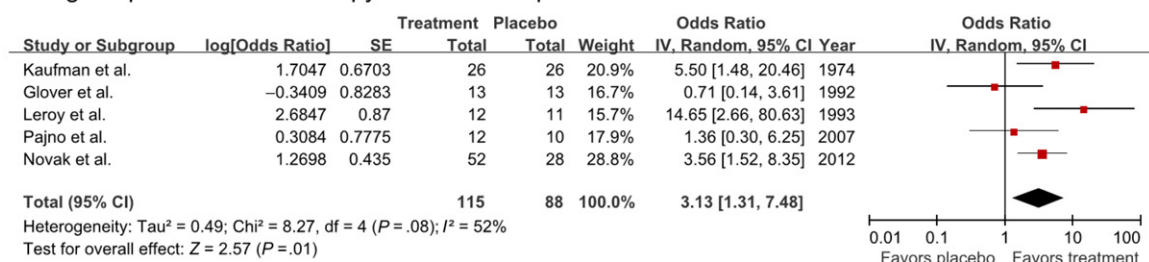
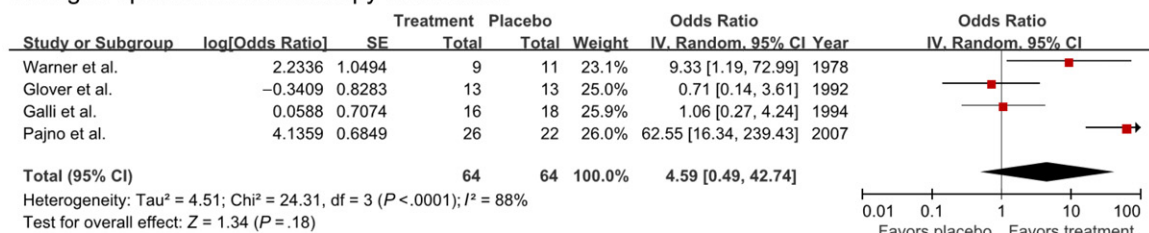
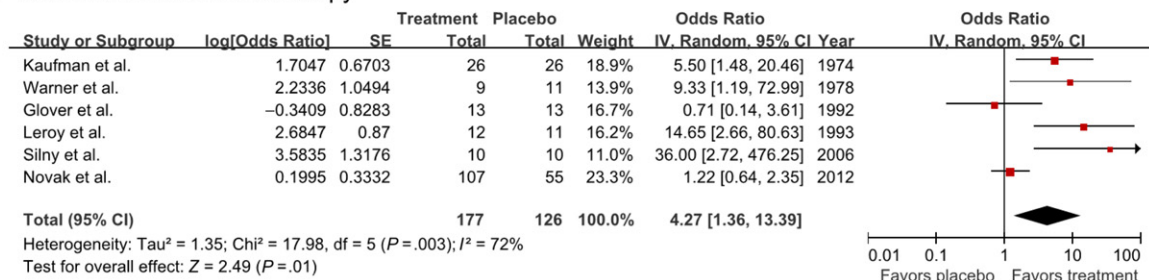
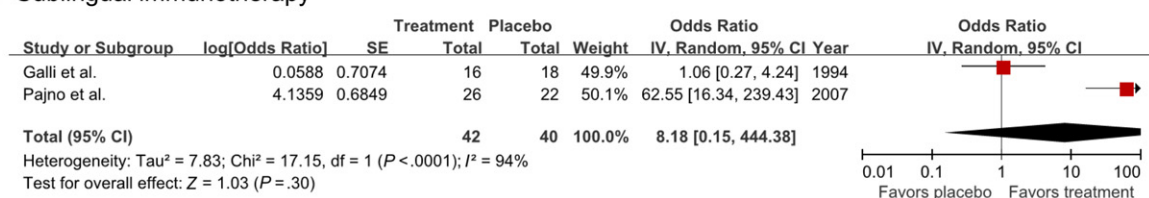
A Long-term treatment over 1 year**B** Allergen-specific immunotherapy for severe atopic dermatitis**C** Allergen-specific immunotherapy for children**D** Subcutaneous immunotherapy**E** Sublingual immunotherapy

FIG 5. Subgroup analyses. **A**, Long-term treatment (more than 1 year). **B**, Allergen-SIT for severe atopic dermatitis. **C**, Allergen-SIT for children. **D**, SCIT. **E**, SLIT.

efficacy. The efficacy of SIT for severe atopic dermatitis is encouraging because the participants all had disease that did not respond to conventional treatment; this subgroup had a lower level of heterogeneity than for the overall study population. Subgroup analyses of SIT for children and of SLIT did not demonstrate significant effects. However, these findings are

preliminary, because the analysis included only a small number of studies and subjects. Furthermore, the use of dichotomous outcomes in interpreting the clinical significance of trial results is problematic because of the intrinsic variability of atopic dermatitis. Dichotomous variables cannot reflect subtle improvements.

TABLE III. Adverse events of allergen-SIT and transient exacerbation of atopic dermatitis

Study, year	Systemic reaction (%)		Local reaction (%)		Transient exacerbation (%)	
	SIT	Control	SIT	Control	SIT	Control
Kaufman and Roth, ²⁴ 1974	NA	NA	50.0	40.0	NA	NA
Warner et al, ²⁵ 1978	NA	NA	NA	NA	48.1	41.7
Glover and Atherton, ²⁶ 1992	0	7.7	NA	NA	46.2	46.2
Leroy et al, ²⁷ 1993	0	0	18.2	54.5	74	83.3
Galli et al, ²⁸ 1994	0	0	6.3	5.6	NA	NA
Silny and Czarnecka-Operacz, ²⁹ 2006	0	0	80.0	60.0	NA	NA
Pajno et al, ³⁰ 2007	7.1	0	7.1	0	14.3	0
Novak et al, ³¹ 2012	8.0	10.7	7.1	10.7	39.3	35.7

NA, Not available.

TABLE IV. Summary of findings for comparison of allergen-SIT and control groups**Patient or population:** Patients with atopic dermatitis**Setting:** Outpatient**Intervention:** Allergen-SIT**Comparison:** Placebo with conventional therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence† (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	SIT				
Treatment success	368 per 1000	757 per 1000 (484-912)	OR 5.35 (1.61-17.77)	385 (8)	⊕ ⊕ ⊕ ⊕ moderate	Appropriate statistical approaches were used for combining dichotomous and continuous outcomes

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†GRADE Working Group grades of evidence:

⊕ ⊕ ⊕ ⊕ High quality: Further research is very unlikely to change our confidence in the estimate of effect.

⊕ ⊕ ⊕ ⊖ Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕ ⊕ ⊖ ⊖ Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕ ⊖ ⊖ ⊖ Very low quality: We are very uncertain about the estimate.

Adverse events were primarily reported as the number of patients who experienced particular events separately; some studies reported the total number of patients with adverse events. These data were not suitable for meta-analysis, and so we performed only a descriptive analysis. Local or systemic reactions were frequently reported, but were usually transient and no fatal adverse events were reported. Acute flares of atopic dermatitis were common and were reported in similar proportions of the SIT and control groups. Flares are unavoidable, but rarely sufficient to withdraw treatment.

SIT modifies allergen hypersensitivity by a variety of mechanisms.^{33,34} Development of tolerance to a specific allergen involves the generation of allergen-specific regulatory T cells, which suppress the T_H2 cell response¹⁶ to reduce the production of IgE; endothelial cell activation; and priming and survival of mast cells, eosinophils, and basophils.⁸ A single administration of allergen-SIT to multisensitized patients with atopic dermatitis patients can thereby downregulate the immune response and reduce symptoms.¹⁶ In addition to increasing numbers of regulatory T cells, SIT can reduce the ratio of allergen-specific IgE:IgG₄ within several months.⁸ Increased proportion of allergen-specific

IgG₄, which blocks the effects of allergen-specific IgE, likely contributes to the clinical efficacy of SIT.³⁵

However, much remains to be learned about the mechanisms by which SIT reduces atopic dermatitis, considering the biphasic nature of the inflammatory response (an initial T_H2 phase followed by a sustained T_H1 cell response in patients with chronic disease).² The induction of tolerance among T_H2 cells cannot completely account for the ability of SIT to reduce symptoms of atopic dermatitis, which involves multiple, complex immune mechanisms.¹⁴

Although our study has several limitations, we demonstrated a statistically significant benefit of allergen-SIT for patients with atopic dermatitis, based on data pooled from 8 RCTs (385 patients). Our results provide physicians with the evidence necessary to consider allergen-SIT for patients with atopic dermatitis, especially those with severe uncontrolled disease. This meta-analysis presents moderate-quality evidence, and further research could influence our confidence in this approach.³⁶ Additional well-designed, double-blind RCTs are needed to confirm the efficacy of SIT; more long-term information is needed to verify that SIT is a disease-modifying therapy

for atopic dermatitis. It will also be essential to learn the precise immune mechanisms of allergen-SIT in atopic dermatitis. Statistical differences may not be of clinical relevance, and more critical issues such as cost-benefit and patient compliance must be evaluated in the clinical field.

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Clinical implications: Based on meta-analysis, allergen-SIT is effective for patients with atopic dermatitis.

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