Specific allergen immunotherapy for the treatment of atopic eczema: a systematic review

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Author contributions:

MC was the contact person with the editorial base at the protocol stage; and RB, at the review stage. MC and RB designed the study and co-wrote the protocol. HN, HW, and SD reviewed earlier drafts of the protocol and provided comments. RB coordinated contributions from the co-authors. HT, MC, LM and RB screened papers against eligibility criteria, appraised the quality of papers, extracted data and sought additional information form original authors. HT, RB, and HN assessed the risk of bias. HT, LM and RB entered data into RevMan, analysed and interpreted data. HT and RB wrote the final draft of the review with contributions from all authors.

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SRD has received research funding for immunotherapy trials in hayfever (but not eczema) via Imperial College from ALK Abello Denmark, Circassia UK and Biotech tools Belgium, all manufacturers of allergy vaccines. He has received consultancy fees via Imperial College from Circassia, Stallergenes, Biomay Austria and Merck USA. The other authors declare no conflict of interest with respect to this publication.

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Background: Specific allergen immunotherapy (SIT) is an effective allergy treatment, but it is unclear whether SIT is effective for atopic eczema (AE). We undertook a systematic review to assess SIT efficacy and safety for treating AE.

Methods: We searched databases, ongoing clinical trials registers, and conference proceedings up to July 2015. Randomised-controlled trials (RCTs) of SIT using standardised allergen extracts, compared with placebo/control for treating AE in patients with allergic sensitisation were eligible.

Results: We identified 12 eligible trials with 733 participants. Interventions included subcutaneous (6 trials), sublingual (4 trials), oral, or intradermal SIT in children/adults allergic to house dust mite (10 trials), grass pollen or other inhalants. Risk of bias was moderate, with high loss to follow-up and non-blinding as the main concerns. For our primary outcomes three studies (208 participants) reported no significant difference - patient-reported global disease severity improvement RR 0.75 (95%CI 0.45, 1.26); eczema symptoms mean difference -0.74 on a 20-point scale (95%CI -1.98, 0.50). Two studies (85 participants) reported a significant difference - SIT improved global disease severity RR 2.85 (95%CI 1.02, 7.96); and itch mean difference -4.20 on a 10-point scale (95%CI -3.69, -4.71). Meta-analysis was limited due to extreme statistical heterogeneity. For some secondary outcomes, meta-analyses showed benefits for SIT eg investigator-rated improvement in eczema severity RR 1.48 (95%CI 1.16, 1.88; 6 trials, 262 participants). We found no evidence of adverse effects. The overall quality of evidence was low.

Conclusion: We found no consistent evidence that SIT is effective for treating AE, but due to the low quality of evidence further research is needed to establish whether SIT has a role in AE treatment.

Introduction:

Atopic eczema (AE) affects 15% to 30% of children and 2% to 10% of adults worldwide, and has a significant quality of life impact(1,2). AE is associated with allergic sensitisation, and can be exacerbated following allergen exposure, suggesting that interventions aimed at reducing allergen-specific responses may be effective for AE treatment(3).

There is high level evidence that SIT reduces symptoms in people with allergic rhinitis, allergic conjunctivitis, asthma and insect sting allergy(4-8). The evidence for SIT as a treatment of AE is less clear(9,10). We undertook a systematic review to evaluate the efficacy and safety of SIT for treating AE, by searching the literature systematically and analysing all evidence arising from randomised controlled trials. A more detailed version of this review will be published and updated in the *Cochrane Database of Systematic Reviews*(11).

Methods:

We conducted systematic searches for all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress). The plans outlining hypothesis and methods were published as a protocol 'Specific allergen immunotherapy for the treatment of atopic eczema'(11).

Search Strategy

We searched the following databases up to July 20, 2015: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library (*2014, Issue 8), MEDLINE (from 1946), Embase (from 1974), LILACS (from 1982), ISI Web of Science (from 2005), the GREAT database (Appendix 2). We searched the following trials registers up to August 3, 2015 using the terms 'immunotherapy and (eczema or dermatitis)': metaRegister of Controlled Trials, U.S. National Institutes of Health Ongoing Trials Register, Australian and New Zealand Clinical Trials Registry, World Health Organization International Clinical Trials Registry platform, and Ongoing Skin Trials Register. We searched abstracts from recent European Academy of Allergy and Clinical Immunology, and the American Academy of Allergy, Asthma and Immunology annual meetings from 2010 to 2015. We checked the bibliography of included studies and review articles for further references to relevant trials. We contacted the primary author of each included study to identify additional published and unpublished studies. We contacted allergen immunotherapy product manufacturers to request details of published or unpublished studies of SIT which have included eczema as an outcome measure.

Selection criteria

We included RCTs studying adults and children with AE and allergic sensitisation to an inhalant or food allergen. Allergic sensitisation needed to be proven using an objective test such as a positive skin prick test or high circulating levels of allergen-specific IgE antibody detected by a specific blood test. Trials focusing on allergic rhinitis or asthma without eczema were excluded(12). Where trials included participants with and without AE, the trial was only included if the results for the participants with AE were reported separately. We included RCTs with intervention using high dose immunotherapy with standardised allergen extracts for single or mixed allergens, administered by the sublingual, subcutaneous, intradermal, or oral route; compared with placebo or standard treatment such as emollients, topical corticosteroids, or topical calcineurin inhibitors. All appropriate allergens were considered at all doses and all durations of treatment. We were interested in both subjective and objective outcomes. Primary outcomes were: participant- or parent-reported global assessment of disease severity at the end of treatment, participant- or parent-reported specific symptoms of eczema, and adverse events. Secondary outcomes were: investigator- or physician-rated global assessment of disease severity at the end of treatment, parent- or participant-rated eczema severity assessed using a published scale, investigator-rated eczema severity assessed using a published scale, use of other medication for treatment of eczema during the intervention period, and validated eczema-related quality of life scores.

Selection of studies

Two authors (RB, and MC or HT) independently checked titles and abstracts identified from the searches, looked at the full text of all studies of possible relevance for assessment, and decided which trials met the inclusion criteria. Any disagreements were resolved by discussion between the authors, and the planned recourse to a third author (HN) for arbitration did not prove necessary. Further information was sought from trial authors when needed to confirm eligibility.

Data extraction

Two authors (RB, and HT or LM) independently extracted data from included trials, and entered data into a specially designed data extraction sheet, and the authors met to compare results. MC, RB, and HT wrote to all authors requesting additional information as required. We contacted authors when details about study design or descriptive statistics for outcomes were not presented in the paper (i.e. mean, SD). If the authors did not respond within a reasonable time (six to eight weeks) to at least two separate written requests for information, we conducted the review based on available information.

Assessment of risk or bias

We assessed and documented the risk of bias in the included studies by concentrating on the following six parameters to assess quality: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting,

and other potential sources of bias as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (19). Three authors (RB, HT, and HN) independently assessed risk of bias: we were not masked to study details. We met to resolve any disagreements, and the planned recourse to a fourth author (MC) for arbitration did not prove necessary. Judgments were reported as 'low risk', 'high risk', or 'unclear risk'.

Measurement of treatment effect

For continuous data we calculated individual and pooled statistics as mean differences (MD) where studies used the same outcome measure, reported with 95% Confidence Interval (CI), where possible. For dichotomous outcomes, we expressed results as a risk ratio (RR) with 95% CI, where possible.

Subgroup analyses

We planned 5 *a priori* subgroup analyses: immunotherapy type (sublingual and subcutaneous); allergen type (seasonal inhalant, perennial inhalant, food, microbial); age of participants (up to 4 years, 5 to 11, 12 to 17, and 18 or over); immunotherapy regimens to be subdivided empirically into low, intermediate, and high dose therapy according to content of major allergen per dose; and AE severity at randomisation.

Assessment of heterogeneity

We tested for heterogeneity using the I^2 statistic and substantial statistical heterogeneity

was defined as $I^2 > 50\%$ (20). Where appropriate, statistical or clinical heterogeneity was explored using sensitivity or subgroup analysis. Quantitative analyses of outcomes were, wherever possible, on an intention-to-treat basis. We analysed continuous outomes using the Mantel-Haenszel method and ~~dicothomous~~ dichotomous outcomes using the inverse variance method. We combined appropriate data from individual studies in a meta-analysis only where heterogeneity measured by $I^2 < 75\%$, using a random-effects model. Where meta-analyses were not applicable, we reported a narrative synthesis of outcomes from relevant studies. We used the GRADE approach for assessing overall quality of evidence contributing to each finding(13).

Sensitivity analyses

Post-hoc sensitivity analyses were not performed due to the small number of studies contributing to meta-analyses.

Results

Our search identified 1556 records (see PRISMA flow diagram Figure 1). Ninety-one records were selected for full text screening. Reasons for rejecting 69 titles were: review article (n=28), not RCT (n=13), not SIT (n=5), not AE (n=12), and no appropriate control (n=6). We found one ongoing trial with no outcome data yet available(14). Overall, 26 reports of 12 separate RCTs with 733 participants met the inclusion criteria(15-26). We contacted all authors for original data and clarification of methods, and received further details for four trials(15,21,24,26).

Characteristics of included studies (Table 1)

Studies were conducted in specialist allergy centres in the UK(17,26), Italy(15,16,22), the USA(18), Germany(21), Belgium(19), Poland(25), Columbia(24), Mexico(20), and China(23). Two studied adults((21,23), six studied children(15-17,20,22,26) and four studied both children and adults(18,19,24,25). Ten studies recruited participants sensitised to *Dermatophagoides pteronyssinus*(15-17,19-24,26), one study house dust mites or grass pollen(25), and one study included allergic sensitisation to a group of unspecified inhalant antigens(18). Six trials used subcutaneous immunotherapy (SCIT)(17,18,21,24-26), four sublingual immunotherapy (SLIT)(15,20,22,23), one intradermal immunotherapy(19), and one oral immunotherapy(16). Eight trials compared intervention with placebo(17-22,25,26) and four with standard treatment(15,16,23,24). Treatment duration was under a year in one trial(19) and at least a year in all others(15-18,20-26).

Risk of bias

Overall the risk of bias was moderate. Risk of performance bias due to non-blinding was high in two open-label studies, both of which reported data for our primary outcome analyses(15,24). There was high attrition bias in eight studies with high loss to follow up (up to 51%) or post-randomisation exclusions(15,17-23). Figure 2 summarises the risk of bias for included studies.

Primary Outcomes

1. Participant- or parent-reported global assessment of disease severity

Warner(26) found improvement in 7/9 (78%) treated with SIT compared with 3/11 (27%) treated with placebo (RR 2.85, 95% CI 1.02 to 7.96; P = 0.04). Glover(17) found improvement in 8/13 (62%) treated with SIT compared with 9/11 (81%) treated with placebo (RR 0.75, 95% CI 0.45 to 1.26; P = 0.38). Meta-analysis was not performed due to high heterogeneity between these two studies (I^2=83%). Pajno(22), found no significant difference reported as a Visual Analogue Score (VAS) between treatment groups but did not report data; and Leroy(19) reported this outcome but not whether there was a significant difference between SIT and control groups. Quality of evidence was low due to heterogeneity (inconsistency) and imprecision.

2. Participant- or parent-reported specific symptoms of eczema

Meta-analyses of two trials with 184 participants(15,21) found no significant reduction in SCORAD C with SIT (MD -0.74, 95% CI -1.98 to 0.50; I^2=0%) or the component parts of SCORAD C - severity of sleep disturbance (MD -0.49, 95% CI -1.03 to 0.06; I^2=0%) and

itch severity (MD -0.24, 95% CI -1.00 to 0.52; I^2 = 0%). A third, non-blinded study(24) found reduced overall symptoms (P < 0.01) and reduced itch severity measured on a VAS from 0-10 (MD -4.20, 95% CI -3.69 to -4.71). Meta-analysis of itch severity data from the three studies was not undertaken due to extreme heterogeneity (I^2 = 98%) attributable to the non-blinded study(24). Data are summarised in Figure 3. Quality of evidence was very low due to study limitations (non-blinding, high loss to follow up), imprecision, and heterogeneity.

3. Adverse events

We found no evidence for adverse effects from trials of SIT used to treat AE. Seven trials(15,17,21-25) with 484 participants reported local adverse reactions: 90/280 (32.1%) participants treated with SIT had a local reaction, compared to 44/204 (34.4 %) with no treatment (RR 1.27, 95% CI 0.89 to 1.81; I^2=25%; Figure 4). Seven trials(15,17,21-25) with 492 participants reported systemic adverse reactions: 18/282 (6.4%) participants treated with SIT had a systemic reaction, compared to 15/210 (7.1%) with no treatment (RR 0.78, 95% CI 0.41 to 1.49; I^2=0%; Figure 4). Quality of evidence was moderate due to imprecision.

Secondary outcomes

1. Investigator- or physician-rated global assessment of disease severity

Meta-analysis of six studies(15,16,18,23-25) with 262 participants, found a significant improvement in disease severity was more likely after SIT than in controls (RR 1.48, 95% CI 1.16 to 1.88; I^2 = 19%; Figure 5). Quality of evidence was very low due to study limitations (non-blinding) and imprecision.

2. Participant or parent-rated eczema severity assessed using a published scale

No study reported this outcome other than those reporting SCORAD part C, which we included as a primary outcome, eczema symptoms.

3. Investigator-rated eczema severity assessed using a published scale

Six studies(15,20-24) with 435 participants reported this outcome as total SCORAD. Meta-analysis of three trials((15,21,24) with 244 participants, showed significant improvement in end of treatment SCORAD (MD -5.79, 95% CI -7.92 to -3.66; $I^2 = 0\%$; Figure 6). Three further studies reported improved SCORAD with SIT. Qin(23) found increased participants with SCORAD change $\geq$ 60% in SIT (77.78%) than control (53.85%) ($P < 0.05$) – we included these data in analysis of investigator- or physician-reported improvement in global severity (Figure 5). Luna-pech(20) found greater reduction in SCORAD with SIT (-18.4 $\pm$ 6.5) than control (-6.6 $\pm$ 4.1; $P = 0.008$). This effect was greater for patients with severe eczema at baseline. Pajno(22) reported greater SCORAD improvement with SIT than control, in graphical data ($P < 0.001$) but no numerical data were available. Glover and Galli(16,17) reported no significant difference using unpublished scales. Quality of evidence was very low due to study limitations (non-blinding, high loss to follow up) and imprecision.

4. Use of other medication for treatment of eczema during the intervention period

Eight studies with 434 participants reported this outcome. Overall 4 studies reported reduced medication use with SIT, and 4 studies reported no significant difference.

Silny(25) reported no statistically significant difference between treatment groups, in the use of topical steroids (RR 1.33, 95% CI 0.74 to 2.41). Glover(17) stated there was no significant difference in the use of topical steroids between treatment groups, without reporting numerical data. Two studies reported the use of systemic steroids for AE. Kaufman(18) found no difference - SIT 8/16 (50%) versus control 4/10 (40%; P = 0.7). Sanchez(24) reported less systemic steroid use with SIT 12/29 (41%) versus control 4/31 (13%; P = 0.02). Meta-analysis was not performed due to high statistical heterogeneity (I^2 = 76%). Novak(21) reported a non-significant 32% difference in the median area under the curve for a medication score combining topical and systemic medication, (19330 SIT, 28420 control; P = 0.08). Pajno(22) reported a significant decrease in frequency (P = 0.03) and days (P = 0.01) of rescue medication use (oral hydroxyzine and topical steroids) with SIT. Luna-Pech(20) reported significantly less use of rescue medications (not defined) in treatment compared to control but no details were provided. Qin(23) reported a lower average daily drug score in treatment (mean 0.5 SD 0.4) than control (mean 1.3 SD 0.7), (P <0.01). Quality of evidence was low, due to study limitations (non-blinding; high loss to follow up) and heterogeneity.

5. Validated eczema-related quality of life scores

Novak(21) reported a validated eczema-related quality of life score, the Dermatology Life Quality Index (DLQI). They found no difference between treatment groups in end of treatment score – SIT median 3.0 (IQR 1.0, 8.0), control 3.5 (1.0, 10.5; P = 0.53).

Subgroup analysis

Subgroup analyses failed to identify a type of immunotherapy, type of allergen, participant age, dose of allergen, or severity of AE with a different efficacy or safety profile, although these analyses were generally inconclusive due to the limited data available. For SCIT vs SLIT, no SLIT data was available for the primary outcome 'participant- or parent-reported global assessment of severity'; no subgroup difference was identified for the primary outcome 'participant- or parent-reported specific symptoms' or 'systemic adverse reactions'; and a subgroup difference for the primary outcome 'local adverse reactions' was identified. We found limited evidence that SLIT is associated with increased local adverse reactions compared to SCIT. Two SLIT studies with 164 participants showed RR 9.76 (95%CI 1.28, 74.26; I^2 = 0%); five SCIT studies with 320 participants showed RR 1.18 (95%CI 0.90, 1.55; I^2 = 0%) – test for subgroup differences P=0.04, I^2 = 75%. For type of allergen, data was only available for one subgroup 'perennial allergen' so no analyses were undertaken. For participant age, data was only available for one subgroup '18 years or over' so no analyses were undertaken. For dose of allergen, no available data were stratified to our planned subgroups so no analyses were undertaken.

Discussion

In this systematic review undertaken within the Cochrane Collaboration, we did not find evidence that SIT is an effective treatment for AE as judged by our pre-specified primary outcomes. The evidence regarding efficacy was marked by inconsistency in study findings, and the overall grade of evidence was low. This suggests a need for further rigorous, well-powered studies to clarify whether SIT has benefits for people with AE.

Our findings contrast with those of a recent systematic review(9), which reported that SIT is effective for treating AE. Odds ratio for improved eczema was 5.35 (95%CI 1.61, 17.77), however the authors combined very heterogeneous outcomes in meta-analysis which may not be appropriate(10), and reported no registered protocol. In another recent systematic review(27), methodological flaws in existing evidence were identified, and the authors' conclusions were similar to ours – that rigorous studies are needed. The authors identified five of the twelve trials included in our review, and an additional two that we excluded because they were not RCTs(28,29).

Although some studies and meta-analyses in our review reported positive findings, the quality of evidence in these analyses was low due to lack of blinding of outcome assessment, high post-randomisation losses to follow up, small study size(s) and inconsistency of findings (Table 3). Meta-analysis was limited due to heterogenous outcome assessments and reporting methods across studies, and confidence intervals were often wide with significant statistical heterogeneity. Some positive meta-analyses were statistically significant, but may not be clinically significant. For example the finding of reduced total SCORAD (Figure 6) was statistically significant, but the 95%CI of this

effect (-7.92, -3.66) excluded the minimal clinically important difference for this outcome measure which is 8.7 points(30). Several outcomes were based on analysis from the trial of Novak(21) with a large number of participants but high loss to follow-up and negative findings. Three trials(15,21,24) had more positive findings than the others, showing a clear beneficial effect on participant- or parent-reported eczema symptoms and investigator- or physician-reported global eczema severity in the form of SCORAD. It is not clear why the findings of these trials differed, especially the trial of Sanchez which used a similar population, intervention, comparator and outcome to the study of Novak. There was however a risk of detection bias due to non-blinding of participants or investigators in the studies of Sanchez and Di Rienzo(15,24).

Although AE is associated with allergic sensitization, it is not solely and directly caused by IgE-mediated allergic responses. Indeed, recent evidence suggests that some allergic sensitization may be a consequence rather than a cause of AE(3,31). The lack of proven efficacy in our study may reflect inappropriately targeting allergens responsible for sensitization but not clinical relevance. Future trials could consider establishing the clinical relevance of sensitisation in study participants, for example using response to allergen exposure in an environmental challenge chamber as an inclusion criterion (3). Treatments directed at the allergic immune response are effective for treating eczema(32), and acute exacerbations of eczema can be precipitated by inhalant allergen exposure in sensitized individuals(3). However environmental stimuli other than inhalant allergens are important causes of eczema exacerbations(33). People with AE often have specific IgE to autoantigens, and high level specific IgE to

microbial antigens(31,34). SIT directed to the inhalant allergens used in the included studies may therefore not be addressing the most important allergenic triggers in many cases. Future trials should consider whether SIT with other allergens may be appropriate.

Adverse reaction rates were not significantly increased with immunotherapy in the included studies, but evidence from other settings suggests that SIT carries a significantly increased risk of severe allergic reactions(4). While this might suggest that the allergic sensitisation to the SIT allergens in the trial participants is of little clinical relevance, or that the allergen extracts used were of low potency, it may equally reflect the small number of trials and participants contributing to the adverse events analysis.

Our ability to explore the dataset for specific groups of patients who might respond better to SIT than others was limited. Data were sparse or absent for pre-specified subgroup analyses, and we were not able to undertake individual patient data meta-analysis. Therefore we cannot exclude the possibility that SIT is effective for specific subgroups of patients with eczema, and this remains an important area to explore in future research studies.

SIT is a well-established treatment with proven efficacy for several allergic diseases. Historically some immunotherapy guidelines have included atopic eczema as a relative contraindication to using SIT. This is not included in current European or North American guidance (35, 36), and we found no evidence to support adverse effects of

SIT when used in patients with eczema.

In conclusion, we found no consistent evidence that SIT provides a treatment benefit for people with AE compared with placebo or no treatment,, however the quality of evidence was low, and study findings were markedly inconsistent. Therefore positive effects for SIT in AE cannot currently be excluded. Further large, rigorously conducted randomised controlled trials using modern high quality allergen formulations with a proven track record in other allergic conditions, which evaluate patient-reported primary outcome measures are needed. Consideration should also be given to the use of non-conventional allergens in SIT for eczema, which may be more relevant to this disease than the classical inhalant allergens.

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Table 1 Characteristics of Included Studies

Trial	Methods	Participants	Intervention (n)	Comparison (n)	Primary Outcome (s) reported	Secondary Outcome (s) reported
Di Rienzo	OL, RCT	57 children aged 5-18 years with (+) SPT and (+) RAST to DF and/or DP, and (+) atopy patch test to HDM, and AE	SLIT DF and DP (30)	No SLIT (27)	Yes	Yes
Galli	RCT	34 children aged 0.5-12 years with (+) SPT and/or (+) RAST to DP and AE	Oral DP (16)	No treatment (18)	No	Yes
Glover	DB, RCT	26 children aged 5-16 years with (+) SPT to DP and severe AE	SCIT DP (13)	Placebo (13)	Yes	Yes
Kaufman	RCT	52 children and adults aged 2-47 years with (+) SPT to mix of inhalant allergens, and uncontrolled AE	SCIT inhalant allergens (25)	Placebo (27)	No	Yes
Leroy	RCT	24 children and adults aged 17-64 years with (+) SPT and (+) sIgE to DP, and AE resistant to environmental treatment	Intradermal DP (13)	Placebo (11)	Yes	Yes
Luna-Pech	DB, RCT	68 children aged 4-10 years with monosensitisation to DP and moderate to severe AD	SLIT DP (34)	Placebo (34)	No	Yes
Novak	DB, RCT	168 adults aged 18-66 with (+) SPT to DP and DF and (+) sIgE to DP or DF, and AE	SCIT DPP (112)	Placebo (56)	Yes	Yes
Pajno	DB, RCT	56 children aged 5-16 years with (+) SPT and (+) RAST to HDM, and AE with SCOARD $\geq$8	SLIT DP and DF (28)	Placebo (28)	Yes	Yes
Qin	?OL, RCT	107 adults aged 18-46 years with (+) SPT to DF, and moderate AE	SLIT DF (58)	Control (49)	Yes	Yes
Sanchez	OL, RCT	65 children and adults aged 3-25 years with (+) sIgE to DF and DP, and AE	SCIT to DPP (32)	Placebo (33)	Yes	Yes
Silny	DB, RCT	20 children and adults aged 5-40 years with (+) SPT and (+) sIgE to HDM or grass, and AE	SCIT DP/DF or grass (10)	Placebo (10)	Yes	Yes
Warner	TB, RCT	56 children aged 5-14 years with asthma, and AE	SCIT DP (28)	Placebo (28)	Yes	No

AE, atopic eczema; DB, double-blind; DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; DPP, DePigmented Polymerized extract; HDM, house dust mite; OL, open-label; SCIT: subcutaneous immunotherapy; SCORAD, SCORing Atopic Dermatitis; sIgE, specific Immunoglobulin E; SLIT, sublingual immunotherapy; SPT, skin prick test; RAST, Radioallergosorbent test; RCT, randomised controlled trial; TB, triple-blind.

Table 2 Summary of Findings for specific immunotherapy compared with no immunotherapy for atopic eczema

Patient or population: adults and children with atopic eczema and inhalant allergen sensitisation **Settings:** specialist allergy centres in UK (2 trials), Italy (3 trials), USA, Germany, Belgium, Poland, Columbia, and China **Intervention:** specific allergen immunotherapy **Comparison:** no immunotherapy						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	No immunotherapy	**Specific allergen immunotherapy**				
Participant- or parent-reported global assessment of disease severity Follow-up: 6 to 12 months	See comments	See comments	Not estimable	44[a] (2)	□□⊖⊖ **low**[b]	Improvement in: 7/9 (78%) immunotherapy and 3/11 (27%) placebo; P = 0.04 (Warner) and 8/13 (62%) immunotherapy and 9/11 (81%) placebo; P = 0.38 (Glover); Unexplained statistical heterogeneity, data not pooled
Participant- or parent-reported specific symptoms of eczema Follow-up: 12 to 18 months SCORAD C measured as combination of two Visual Analog Scale (one for itch, one for sleep disturbance), each on a scale from 0, no symptoms, to 10, maximum symptoms	The mean SCORAD C score ranged across control groups from **3.07 to 5.29** The mean SCORAD C sleep severity score ranged across control groups from **0.8 to 2.31** (Di Rienzo; Novak)	The mean SCORAD C score in the immunotherapy group was on average **0.74 lower (95% CI -1.98 to 0.50)** The mean SCORAD C sleep severity score in the immunotherapy group was on average **0.49 lower (95% CI -1.03 to 0.06)** (Di Rienzo; Novak)		339[a] (6)	□⊖⊖⊖ **very low**[c]	Itch: SCORAD C itch severity at the end of treatment: MD -0.24, 95% CI -1.00 to 0.52; I^2 = 0% for (Di Rienzo) and (Novak) Itch severity score: MD -4.20, 95% CI -3.69 to -4.71 for Sanchez 2012. Unexplained statistical heterogeneity, data not pooled
Adverse events - any systemic reaction Follow-up: 6 to 18 months	**Low risk population**		**RR 0.78 (**0.41 to 1.49)	492[a] (7)	□□□⊖ **moderate**[d]	
	0 per 1000	**0 per 1000** (0 to 0)				
	Medium risk population					
	71 per 1000	**55 per 1000** (29 to 106)				
	High risk population					
	163 per 1000	**127 per 1000** (67 to 243)				
Investigator- or physician-rated global assessment of disease severity Follow-up: 1 to 3 years	**Low risk population**		**RR 1.48 (**1.16 to 1.88)	286[a] (7)	□⊖⊖⊖ **very low**[e]	
	0 per 1000	**0 per 1000** (0 to 10)				
	Medium risk population					
	471 per 1000	**697 per 1000** (546 to 885)				
	High risk population					
	778 per 1000	**1151 per 1000** (903 to 1462)				
Investigator- or	The mean SCORAD	The mean SCORAD		435[a]	□⊖⊖⊖	

physician-rated eczema severity using a published scale Follow-up: 12 to 18 months	score ranged across control groups from **26.7 to 32.6** (Di Rienzo; Novak; Sanchez)	score in the immunotherapy group was on average **5.79 lower** **(95% CI -7.92 to -3.66)** (Di Rienzo; Novak; Sanchez)		(6)	**very low**[f]	

GRADE: Grading of Recommendations Assessment, Development and Education; **CI:** Confidence interval; **RR:** Risk Ratio.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) 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.

Assumed risks are based on the total control group risk across all included studies (medium-risk population) and the included studies with the lowest (low-risk population) and highest (high-risk population) control group risks.

a. The number of total participants did not include those there were lost to follow-up. The number of participants and trials included those that contributed to narrative synthesis.

b. Reasons for downgrading: unexplained heterogeneity (serious, -1), and imprecision (serious, -1). There was significant heterogeneity (I^2 = 83%) between the estimate of treatment effects in the two studies (Warner and Glover) and data was not pooled. The information size is small.

c. Reasons for downgrading: study limitations of the study design (serious, -1), imprecision (serious, -1), and unexplained heterogeneity (serious, -1). Two trials were non-blinded. Moderate proportions of participants were not analysed (losses to follow up). The information size is small. Most subgroups of estimate of treatment effects were not statistically significant with itch displaying high heterogeneity (I^2 = 98%). Data were not pooled due to different symptoms and different scoring systems reported.

d. Reason for downgrading: imprecision (serious, -1). The estimate of treatment effect relied largely on one study. It is unclear whether the estimate obtained from a small number of adverse reactions to a single dust mite extract in this study can be generalised. Indeed data from other populations suggest that specific allergen immunotherapy is generally associated with a small but significant risk of systemic adverse reactions.

e. Reason for downgrading: study limitations (serious, -2), and imprecision (serious, -1). The estimate of treatment effect relied on two non-blinded studies. The information size is small.

f. Reason for downgrading: study limitations (serious, -2), and imprecision (serious, -1). Two studies were non-blinded. Moderate proportions of participants were not analysed (losses to follow up). The information size is small.

Table 3 Limitation of meta-analyses

Limitation	Details	Implication for Future Studies
Small studies	**N<100 for 10/12 studies**	**Larger enrolment**
Heterogeneous outcomes	**Variability in reported outcomes in included studies**	**Evaluate patient-reported primary outcomes**
Risk of bias	**Open-label studies** **High loss to follow-up** **Funding from manufacturer**	**Double-blinded, randomized controlled trials** **Stringent methodology** **A priori protocol**
Subgroup analyses	**Insufficient evidence to assess differences between subgroups**	**Larger trials with standard subgroup stratification to enable meta-analyses**
Assess clinically relevant allergy	**Included patients with allergen sensitization but not challenge-proven AE exacerbations**	**Establishing challenge-proven exacerbation such as using a challenge chamber**

Figure Legends

Figure 1. PRISMA flow diagram. AE, atopic eczema; RCTs, randomised controlled trials; SIT, specific allergen immunotherapy

Figure 2. Risk of bias in included studies. The Cochrane Risk of Bias tool was used to assess risk of bias in included studies. Green represents low risk, yellow unclear risk, red high risk of bias.

Figure 3. Forest plots of participant- or parent-reported specific symptoms of eczema

Figure 4. Meta-analyses of adverse events

Figure 5. Meta-analyses of investigator- or physician-rated global disease severity

Figure 6. Meta-analyses of investigator rated eczema severity using a published scale