

Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: A systematic review and indirect comparison

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Background: Severe allergic rhinitis uncontrolled by pharmacotherapy can adversely affect quality of life. Both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have demonstrated effectiveness in this patient group; however, it remains uncertain which route of administration is more effective.

Objectives: We sought to update existing systematic reviews on the clinical effectiveness of SCIT and SLIT versus placebo, to undertake a systematic review of head-to-head trials, and to compare the relative effectiveness of SCIT and SLIT in an adjusted indirect comparison.

Methods: Standard systematic review methods aimed at minimizing bias were used. Double-blind, randomized, placebo-controlled trials of SCIT or SLIT or trials of SCIT versus SLIT were included. Meta-analysis and indirect comparison meta-analysis with meta-regression were performed.

Results: Updated meta-analyses confirmed statistically significant benefits for SCIT and SLIT compared with placebo in adults and, to a lesser extent, in children. Only 1 head-to-head trial met the inclusion criteria; both this and the indirect comparisons did not provide conclusive results in favor of either SCIT or SLIT based on symptom-medication or quality-of-life scores. There was a trend toward favoring SCIT for symptom and medication scores.

Conclusions: Although there is clear evidence of effectiveness of both SCIT and SLIT, superiority of one mode of administration over the other could not be consistently demonstrated through indirect comparison, and further research is needed to establish the comparative effectiveness of SCIT versus SLIT. (*J Allergy Clin Immunol* 2013;■■■:■■■-■■■.)

Key words: Allergic rhinitis, sublingual immunotherapy, subcutaneous immunotherapy, systematic review, meta-analysis, indirect comparison, meta-regression

Allergic rhinitis (AR) is a global health problem that affects patients from all ethnic groups, socioeconomic conditions, and ages. The prevalence of positive skin test responses to an outdoor allergen (eg, grass and tree pollen) among the US population has been estimated at 40%.¹ Severe AR has a large effect on health-related quality of life, work, and educational performance, which results in a significant individual and economic burden. AR and asthma are frequently comorbid conditions. Both disorders affect the mucosal lining of the respiratory tract, are linked by common underlying cellular processes, and thus might be considered part of the same allergic disease (“united airways” approach).² There is widespread evidence to suggest that AR in children often predicts the development of asthma.³

Pharmacotherapy provides symptomatic relief. However, some patients are unable to tolerate pharmacotherapy, and a substantial number report only partial or poor symptom control, particularly of systemic symptoms (eg, fatigue or headache).^{4,5} Both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are increasingly being considered for this patient group.^{6,7} In contrast to pharmacotherapy, the clinical benefits of SCIT and SLIT appear to be sustained after cessation of treatment.⁸⁻¹¹ As well as treating symptoms, there is evidence that immunotherapy can prevent disease progression, development of new sensitizations, and onset of asthma.^{2,6}

There are no explicit guidelines on when SCIT or SLIT should be the preferred treatment option. Historically, the method of administration has been subcutaneous. However, SCIT has been associated with a perceived higher risk of adverse events; it might be for this reason that, in the United Kingdom at least, SLIT is more commonly prescribed in children.¹² Choice of treatment might depend on patient’s or physician’s preference, with SCIT being more resource intensive because it has to be administered in a clinical setting.

There are numerous reviews of immunotherapy, the most comprehensive being 2 Cochrane Reviews of placebo-controlled randomized controlled trials (RCTs) of SCIT (Calderon et al¹³) and SLIT (Radulovic et al¹⁴). Pooled standardized mean differences (SMDs) from meta-analyses found statistically significant results in favor of active treatment across all outcomes measured (including symptom scores, medication scores, and quality of life).

Although there is now substantial evidence of the effectiveness of SCIT and SLIT, respectively, compared with placebo, direct head-to-head evidence of SCIT versus SLIT is sparse, and we identified no systematic reviews of such trials. No indirect comparisons of SCIT versus SLIT were identified. Our objective

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This work formed part of a wider project commissioned and funded by the UK National Institute for Health Research Health Technology Assessment Programme as project no. 09/78/01.

Disclosure of potential conflict of interest: J. Dretzke, A. Meadows, N. Novielli, A. Fry-Smith, and C. Meads have received research support from the National Institute for Health Research Health Technology Assessment Programme. A. Huissoon has received consultancy fees from the Meda advisory board, has received lecture fees from and holds stock in GlaxoSmithKline, has received travel support from ALK-Abelló, and ALK-Abelló and Meda Pharmaceuticals have sponsored annual allergy training meetings that his department organizes for primary care physicians.

Received for publication October 11, 2012; revised January 23, 2013; accepted for publication February 14, 2013.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2013.02.013>

Abbreviations used

AR:	Allergic rhinitis
CrI:	Credible interval
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT:	Randomized controlled trial
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
SMD:	Standardized mean difference
SSD:	Standardized score difference

was therefore to update the existing Cochrane Reviews, conduct a systematic review of head-to-head trials of SCIT versus SLIT, and undertake an indirect comparison analysis of SCIT versus SLIT based on up-to-date meta-analyses. Both adults and children were considered.

METHODS

Systematic review methodology and reporting were based on the Cochrane Collaboration handbook¹⁵ and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).¹⁶ Double-blind RCTs of SCIT or SLIT versus placebo or of SCIT versus SLIT were sought. Studies were eligible if they included adults or children with moderate-to-severe seasonal AR (with or without asthma) and patient-related outcomes.

Bibliographic databases were searched to April 2011 with no language restrictions (MEDLINE, EMBASE, Cochrane Library [CENTRAL], CINAHL, and Science Citation Index; see the [Methods](#) section in this article's Online Repository at www.jacionline.org for full search strategies). Ongoing trial registers and reference lists of relevant studies were checked, and clinical experts were consulted. Potentially relevant studies were independently screened for inclusion by 2 reviewers, obtaining the full text where necessary. Discrepancies were resolved through discussion or referral to a third reviewer.

Cochrane Collaboration guidelines¹⁷ were followed for risk of bias assessment, with the following criteria considered: adequate sequence generation, concealment of allocation, blinding of patients/personnel, completeness of outcome data, selective reporting of outcomes, and immunotherapy treatment history. Blinding of outcome assessors was not assessed because outcomes were largely patient reported. Each item was classified as having a low, high, or unclear risk of bias. Data extraction, including risk of bias assessment, was conducted by one reviewer and checked by a second using a standard, piloted extraction form. Discrepancies were resolved through discussion. Results from studies previously reported in the Cochrane Reviews were not checked.

Statistical methods: SCIT or SLIT versus placebo

Meta-analyses from the Cochrane Reviews were updated, where possible. These were limited to commonly reported outcomes in which suitable data were provided or calculable (ie, symptom scores, medication scores, combined symptom-medication scores, and quality-of-life scores). Results not suitable for meta-analyses were tabulated and described.

Meta-analyses were undertaken in RevMan (5.1)¹⁸ by using a random-effects model. SMDs were presented because there was little overlap in how outcome scores were calculated across trials. As a rule of thumb, SMDs (effect sizes) can be described as small (<0.4), moderate (0.4-0.7), or large (>0.7).¹⁹

Statistical methods: SCIT versus SLIT

Indirect comparison meta-analysis and indirect comparison meta-regression were conducted in WinBUGS 1.4²⁰ to compare the effectiveness of SCIT versus SLIT for each of the 4 main outcomes.

An indirect comparison relies on the assumption that there is sufficient similarity both within and between the trial sets.²¹ Similarity of trial and population characteristics within and between SCIT versus placebo and SLIT

versus placebo trials was assessed qualitatively and statistically. Possible sources of heterogeneity were explored and adjusted for in a meta-regression by using the following covariates: participant age (adult/child), treatment duration (<6, 6-12, and >12 months), major allergen content of immunotherapy product (<5, 5-20, and >20 µg), and type of allergen (grass, tree, *Parietaria* species, *Alternaria* species, and ragweed). A random-effects model was used to take account of a degree of unexplained heterogeneity in the data. Improvement in model fit was expressed by using the Deviance Information Criteria, a compound measure of model fit and complexity, and extent of residual variation was recorded. Standardized score differences (SSDs) and 95% credible intervals (CrIs) were calculated to estimate the difference in effect size between SCIT and SLIT; positive values favor SCIT, and negative values favor SLIT. Probabilistic analysis also allowed calculation of best estimate probabilities. These show the probability of either SLIT or SCIT being the best treatment, but do not provide information on the relative effectiveness of treatments.

A full description of the methods is provided in the [Methods](#) section in this article's Online Repository.

RESULTS

Seventeen placebo-controlled RCTs for SCIT and 11 for SLIT were identified (postdating the Cochrane Reviews' search dates). Five studies for SCIT and SLIT, respectively, contributed to updating the Cochrane meta-analyses (see [Fig 1](#) for the PRISMA flow diagram). RCTs were heterogeneous in terms of type of allergen, major allergen content, administration schedule, study size, duration of treatment, and outcomes assessed. Only 1 relevant head-to-head trial (SCIT vs SLIT) was identified.

Trial quality

Assessment of risk of bias was hampered by a lack of reporting of relevant criteria, but although the risk of bias was frequently unclear, there were very few instances of high risk of bias.

SCIT versus placebo

Statistically significant results favoring SCIT were found for symptom scores (SMD, -0.65; 95% CI, -0.85 to -0.45; $P < .00001$; 17 trials), medication scores (SMD, -0.55; 95% CI, -0.75 to -0.34; $P < .00001$; 16 trials), symptom-medication scores (SMD, -0.48; 95% CI, -0.67 to -0.29; $P < .00001$; 8 trials), and quality-of-life scores (SMD, -0.53; 95% CI, -0.66 to -0.39; $P < .00001$; 8 trials). Subgroup analyses by age, study duration, major allergen content, and type of allergen all favored the active treatment, and all but one (ie, subgroup analysis by major allergen content <5 µg for medication scores) were statistically significant. Subgroup analyses suggested an increased benefit with greater allergen content. All but 1 trial were conducted in adults; one small pediatric trial²² ($n = 50$) found a statistically significant reduction in symptom and medication scores with SCIT after 3 years of treatment (see [Figs E1-E4](#) in this article's Online Repository at www.jacionline.org for Forest plots).

SLIT versus placebo

Statistically significant results favoring SLIT were found for symptom scores (SMD, -0.33; 95% CI, -0.42 to -0.25; $P < .00001$; 42 trials), medication scores (SMD, -0.27; 95% CI, -0.37 to -0.17; $P < .00001$; 35 trials), and quality-of-life scores (SMD, -0.37; 95% CI, -0.52 to -0.22; $P < .00001$; 7 trials). The previous Cochrane Review did not analyze combined medication-symptom scores; a statistically significant result

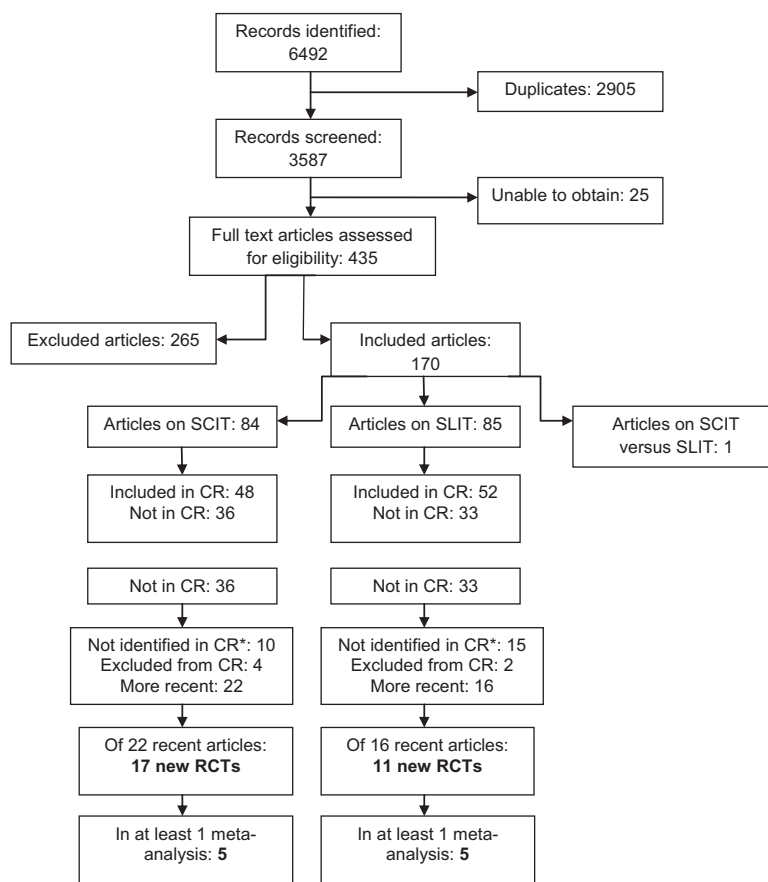


FIG 1. PRISMA flow diagram of the study selection process. CR, Existing Cochrane Reviews on SCIT and SLIT, respectively. *Studies that had not been identified in the previous Cochrane Reviews were in the main duplicate publications (eg, in abstract form) of included studies.

favoring SLIT was also found for this outcome (SMD, -0.40 ; 95% CI, -0.55 to -0.25 ; $P < .00001$; 6 trials). Overall, the effect sizes appeared slightly lower than for SCIT versus placebo. Sub-group analyses all favored the active treatment, and the vast majority were statistically significant. Medication scores were not significantly improved in pediatric patients on active treatment compared with those on placebo (8 studies, total $n = 1175$; see Figs E5-E8 in this article's Online Repository at www.jacionline.org for Forest plots).

Adverse events

Adverse events were common in both SCIT and SLIT, but the majority were local reactions, which resolved spontaneously. Systemic reactions were less common, and most were graded as mild or moderately severe. However, 19% of systemic reactions after SCIT treatment were considered to be severe compared with only 2% of systemic reactions after SLIT (based on studies that reported this information). Discontinuations because of adverse events (approximately 3%) were similar between the interventions. No fatalities were reported.

Head-to-head trials

Searches identified only 1 randomized, double-blind study ($n = 71$) of SLIT versus SCIT.²³ Three further studies were

initially identified as potentially relevant but subsequently excluded for inadequate blinding^{24,25} or apparently inadequate randomization.²⁶ No study reported significant differences between SCIT and SLIT.

Indirect comparison

Overall, inclusion criteria (where reported) and patients' characteristics appeared similar between the SCIT and SLIT populations (in terms of allergy history, severity, and prevalence of asthma). All studies excluded patients with severe or perennial asthma. However, there was variation in trial duration, type and amount of allergen, and statistical evidence of moderate heterogeneity in the meta-analyses for some outcome measures ($I^2 = 57\%$ for symptom score and medication score [SCIT vs placebo]; $I^2 = 59\%$ for quality of life [SLIT vs placebo]). In view of this heterogeneity, we adjusted for a number of covariates.

SCIT versus SLIT: Symptom score. The overall SSD was 0.351 (95% CrI, 0.127-0.586), a statistically significant result in favor of SCIT. SSDs adjusted for covariates mostly favored SCIT, and some were statistically significant (adults, trial duration <6 months, major allergen content >20 μg , grass, *Parietaria* species). Probabilistic analysis suggested that SCIT had a greater probability of being the best treatment compared with SLIT overall and also when accounting for participant's age, study duration, major allergen content, and type of allergen.

However, residual heterogeneity in the model could not be accounted for by participant's age, type of allergen, or trial duration; only major allergen content as a covariate reduced heterogeneity slightly.

A *post hoc* meta-regression was conducted to explore unexplained residual heterogeneity further, with year of publication used as a covariate. Year of publication might be considered a proxy for changes over time in treatment protocols, trial methodologies (eg, patient selection or methods of data gathering), or other unknown variables. An improvement in the fit of the model to the data was observed, with heterogeneity also slightly reduced. As shown in Fig 2, the probability of SCIT being more effective shifts to SLIT being more effective over time, with the probabilities crossing over from approximately 2007. However, it should be noted that SSDs at different time points were not all statistically significant and that the relative probabilities are not a measure of relative effectiveness. See the Results section in this article's Online Repository at www.jacionline.org for full results of indirect comparisons.

SCIT versus SLIT: Medication score. The overall SSD was 0.273 (95% CrI, 0.027-0.529) in favor of SCIT. The 2 statistically significant adjusted SSDs (grass, trial duration >12 months) also favored SCIT. The overall score was associated with a greater than 99% chance of SCIT being the best treatment. Where adjusted analyses resulted in SSDs in favor of SLIT, these were not statistically significant. A large proportion of heterogeneity could be reduced by introducing major allergen content and particularly age (adult/child) as a covariate; however, the results adjusted for these covariates were not statistically significant.

SCIT versus SLIT: Combined symptom-medication score. No significant differences could be shown for symptom-medication scores, and this was associated with a large degree of uncertainty, as reflected in the wide CrIs (SSD, 0.313; 95% CrI, -195.8 to 194.1). Best estimate probabilities found that SCIT and SLIT had a roughly equal probability of being the best treatment. There was less heterogeneity associated with this analysis (compared with symptom and medication scores separately), and this was further reduced when type of allergen was introduced as a covariate.

SCIT versus SLIT: Quality of life. Results for quality-of-life scores found that although there was a high probability of SCIT being the best treatment, the overall SSD was not statistically significant (SSD, 0.383; 95% CrI, -0.042 to 0.804) and was associated with a high degree of heterogeneity. None of the adjusted SSDs were statistically significant. See Tables E1-E10 in this article's Online Repository at www.jacionline.org for full results of the indirect comparisons.

DISCUSSION

This update of existing Cochrane Reviews used a robust review methodology, including a comprehensive search strategy, and it is unlikely that many relevant studies were missed. As far as we are aware, this is the first time a systematic search for head-to-head trials and a formal indirect comparison have been conducted.

Updated meta-analyses

A total of 28 new double-blind, placebo-controlled RCTs of SCIT ($n = 17$) or SLIT ($n = 11$) were identified. We did not use a

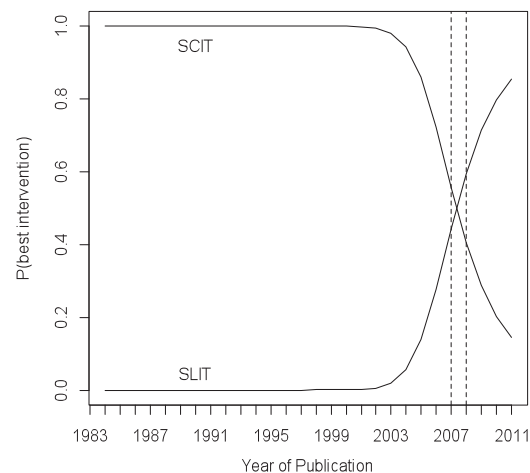


FIG 2. Probability of either SCIT or SLIT being the best treatment based on symptom scores and using year of publication as a covariate in the indirect comparison meta-regression.

quality threshold for including studies because quality criteria were often poorly reported, and inclusion would therefore have been on the basis of reporting rather than actual quality. Overall, we gauged that the results were unlikely to be affected substantially by the few studies reporting instances of high risk of bias, but variation in methodological quality remains a potential source of heterogeneity.

The total number of participants in the updated meta-analyses increased only slightly compared with the Cochrane Reviews, and results were very similar, with both SCIT and SLIT being statistically significantly more effective than placebo across the 4 outcomes.

In SCIT improvements in both symptom and medication scores increased with higher vaccine allergen content, which is consistent with the recognized dose-response relationship. This is based on nonrandomized comparisons from subgroup analyses and should therefore be interpreted cautiously.

Data on children are still relatively sparse. Only one study on SCIT was included in meta-analyses, which found a statistically significant benefit for immunotherapy after 3 years of treatment (symptom score, medication score, and quality of life).²² For SLIT, medication scores in children still did not show a significant improvement with active treatment (8 trials), although there was a statistically significant difference for symptom scores (9 trials) and quality of life (1 trial). The clinical significance of this finding is unclear; the medication score in isolation might not be able to reflect the effectiveness of SLIT.

None of the trials in children take into consideration potential future benefits from immunotherapy, such as avoidance of asthma or new sensitizations. The Grazax Asthma Prevention RCT,²⁷ which is due to complete in 2015, has randomized children with AR and no asthma to SLIT or placebo; asthma symptoms are included as a primary outcome measure.

Limitations

Only studies with consistently used outcome measures were included in the direct and indirect comparison meta-analyses. However, although many relevant studies did not contribute to the pooled estimates, findings were similar to those included (ie,

benefit from immunotherapy over placebo). For example, the largest of the new trials identified for SCIT versus placebo (DuBuske et al,²⁸ $n = 1028$) expressed outcomes as numbers of “well days” and “bad days.” This study evaluated the effect of an ultrashort course of SCIT and found significant benefits for SCIT over a 4-week period.

The 6 major European manufacturers all use different scoring systems for deriving symptom scores, medication scores, and combined symptom-medication scores.²⁹ A consequence of variable scoring, even where the same outcome measure is used, is that the pooled summary measures from meta-analyses can only be reported as SMDs, which are difficult to interpret clinically. There is currently no consensus on a clinically meaningful minimum change on a specific outcome measure, although various cutoff points have been suggested.^{30,31}

The Core Outcome Measures in Effectiveness Trials Initiative³² is attempting to develop standardized sets of outcomes, which represent the minimum that should be reported in all clinical trials of a specific condition. However, immunotherapy is an area that has not (yet) been addressed. Ultimately, this would make it easier for the results of trials to be compared and combined.

The effect of immunotherapy in patients with severe uncontrolled AR was of particular interest when conducting this review; however, disease severity was not always reported, and it is conceivable that there was a degree of variation across trials. The concept of severe chronic upper airway disease has recently been proposed³³; this defines patients with uncontrolled AR despite adequate pharmacologic treatment based on guidelines and has potential as an inclusion criterion in future trials.

Indirect comparisons

In contrast to the large number of placebo-controlled trials, only 1 small, double-blind, head-to-head RCT of SCIT versus SLIT was identified, and therefore an indirect comparison was justified.

In assessing similarity between trial populations, it would have been of interest to compare rates of response of the SCIT and SLIT placebo groups. However, it was not possible to compare these directly because of (1) use of different outcome measures and (2) the fact that any differences between baseline and follow-up are likely to differ between studies conducted at different times and geographic areas because of variations in pollen count. Although placebo rates could be expected to be similar in comparable populations, there is also evidence from other clinical areas that placebo rates can differ according to method of administration.³⁴ With placebo being administered sublingually or subcutaneously and at different frequencies (daily for sublingually and weekly and then monthly for subcutaneously), this might be the case here. However, no evidence was identified to either confirm or refute this hypothesis, and failing to make the assumption of comparable placebo rates would have precluded an indirect comparison analysis.

Because there was some evidence of heterogeneity, indirect comparison meta-regression with various covariates was performed to explore and potentially reduce this heterogeneity. Overall, there was a trend toward favoring SCIT based on symptom and medication scores. However, any statistically significant findings were typically associated with fairly substantial residual heterogeneity, suggesting that we did not account for

all sources of heterogeneity (potentially study quality or population characteristics other than age).

In the analyses using combined symptom medication scores and quality-of-life scores, arguably preferred outcome measures, none of the differences were statistically significant but were associated with reduced heterogeneity. SLIT RCTs reporting these latter outcome measures are all relatively recent (from 2006 onwards), and changes in treatment protocols or study design might be contributing to an apparently greater efficacy of SLIT relative to SCIT in more recent years.

This trend is also reflected in the fact that year of publication appeared to account for a degree of heterogeneity (for symptom scores). Probabilistic analyses were suggestive of SCIT being associated with a greater probability of being the best treatment in earlier studies compared with studies published at a later date, which found a greater probability for SLIT. However, these results are based on use of a *post hoc* defined variable on 1 outcome measure only (symptom score) and must therefore be considered exploratory in nature.

The use of an SSD makes interpretation problematic, and where significant differences were found favoring SCIT, it is difficult to gauge how much of a clinical difference this would make. Overall, it was difficult to draw firm conclusions from these results because they (1) vary depending on which outcome measure is used and (2) are associated in some instances with substantial residual heterogeneity despite adjusting for covariates. A more useful dataset would include studies using only validated standardized outcome measures and treatment regimens.

Future research recommendations

Given the difficulties in comparing and combining results across studies using different outcome measures, there is a clear need for greater consistency in the use of validated outcome measures, which should take into consideration that the relative effectiveness of immunotherapy compared with symptomatic medication varies depending on prevailing allergen levels.

We did not specifically address optimum dosing and treatment regimens or the efficacy of different immunotherapy products (eg, modification of the allergen extract with adjuvants and use of allergen fragments). Ultrashort immunotherapy treatment schedules have shown promise in terms of clinical efficacy, and they place considerably less burden on patients in terms of time and inconvenience. However, little evidence currently exists regarding sustained benefit beyond treatment cessation.

In view of the limitations of the indirect comparison analysis in this report, consideration should be given to a head-to-head trial of SCIT versus SLIT. Searches for ongoing trials identified only 1 double-blind trial of SLIT versus SCIT due for completion in 2014.³⁵ It is unclear why direct comparisons are so sparse; reasons might include a reluctance on the manufacturer's part to directly compare commercial products or methodological issues regarding double-blinding of such trials. For both SCIT and SLIT, at present, the most appropriate treatment regimens to be compared would be those with 3-year protocols because this is where the best evidence exists regarding long-lasting efficacy.

We thank Dr Duncan Wilson for input into the review protocol and clinical advice, Dr M. Thirumala Krishna for input into the review protocol, and Dr Karla Hemming for advice and comments on statistical aspects.

Key messages

- Effectiveness of both SCIT and SLIT compared with placebo has been consistently demonstrated, particularly for adults. The extent of this effectiveness in terms of clinical benefit remains unclear, with interpretation hampered by inconsistent use and uncertainty around the most appropriate outcome measures.
- There is a dearth of head-to-head trials in this area. Only 1 head-to-head trial met the inclusion criteria, and neither this nor the indirect comparisons provided conclusive results in favor of either SCIT or SLIT based on symptom-medication or quality-of-life scores, although there was a trend toward favoring SCIT based on symptom and medication scores.
- Indirect comparisons were hampered by heterogeneity despite attempts to adjust for this, and further research is needed to establish the comparative effectiveness of SCIT versus SLIT.

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Search Strategies

Clinical Effectiveness

Source – Cochrane Library (CENTRAL) 2011 Issue 1

- #1 MeSH descriptor Rhinitis, Allergic, Seasonal, this term only
- #2 (rhinoconjunctivitis or rhino next conjunctivitis)
- #3 hay next fever
- #4 pollen next allergen*
- #5 season* next allergic
- #6 hayfever or pollinosis or pollenosis or sar
- #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
- #8 MeSH descriptor Rhinitis, this term only
- #9 rhinitis
- #10 (#8 OR #9)
- #11 intermittent* or season* or spring or summer
- #12 pollen* or grass* or birch or ragweed or tree*
- #13 weed* or mugwort or willow or alder
- #14 MeSH descriptor Trees, this term only
- #15 (#11 OR #12 OR #13 OR #14)
- #16 (#10 AND #15)
- #17 MeSH descriptor Desensitization, Immunologic, this term only
- #18 MeSH descriptor Allergens, this term only
- #19 desensiti* or hyposensiti*
- #20 MeSH descriptor Immunotherapy, this term only
- #21 immunotherap* or immunomodulatory or allergen* or antigen*
- #22 immune next therapy
- #23 immunologic next response*
- #24 grazax or pollinex or alutard
- #25 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
- #26 (#7 OR #16)
- #27 (#25 AND #26)

Source – Ovid MEDLINE(R) 1948 to April Week 2 2011

- 1 Rhinitis, Allergic, Seasonal/ (11107)
- 2 (rhinoconjunctivitis or rhino conjunctivitis).ti,ab. (1334)
- 3 (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season* allergic).ti,ab. (13935)
- 4 or/1-3 (22044)
- 5 Rhinitis/ (7156)
- 6 rhinitis.ti,ab. (15813)
- 7 or/5-6 (19981)
- 8 (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab. (223342)
- 9 Trees/ or Poaceae/ (23581)
- 10 8 or 9 (234891)
- 11 7 and 10 (3812)
- 12 Desensitization, Immunologic/ (7170)
- 13 allergens/ (28104)
- 14 (desensiti* or hyposensiti*).ti,ab. (22895)
- 15 immunotherapy/ (25148)
- 16 (immunotherap* or immunomodulatory or immune therapy or immunologic response* or allergen* or antigen*).ti,ab. (509932)
- 17 (grazax or pollinex or alutard).ti,ab. (101)
- 18 or/12-17 (552055)
- 19 4 or 11 (23106)
- 20 18 and 19 (7716)
- 21 exp animals/ not humans/ (3565261)
- 22 20 not 21 (7358)
- 23 limit 22 to "therapy (optimized)" (1051)

Source – EMBASE (Ovid) 1980 to 2011 Week 15

- 1 exp allergic rhinitis/ (22724)
- 2 (rhinoconjunctivitis or rhino conjunctivitis).ti,ab. (2038)
- 3 (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season* allergic).ti,ab. (16538)
- 4 or/1-3 (35766)
- 5 rhinitis/ (11928)
- 6 rhinitis.ti,ab. (20790)
- 7 or/5-6 (27861)
- 8 (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab. (278114)
- 9 tree/ or grass pollen/ (16418)
- 10 or/8-9 (284179)
- 11 7 and 10 (5386)
- 12 desensitization immunologic/ (13113)
- 13 allergen/ (31586)
- 14 (desensiti* or hyposensiti*).ti,ab. (25828)
- 15 immunotherapy/ (38113)
- 16 (immunotherap* or immunomodulatory or immune therapy or immunologic response* or allergen* or antigen*).ti,ab. (552975)
- 17 (graxax or pollinex or alutard).ti,ab. (191)
- 18 or/12-17 (604305)
- 19 4 or 11 (36735)
- 20 18 and 19 (12139)
- 21 exp animal/ not human/ (1254356)
- 22 20 not 21 (12046)
- 23 limit 22 to "treatment (2 or more terms min difference)" (1982)

Source – CINAHL (EBSCOhost) 1982 - 2011

- S1
(MH "Rhinitis, Allergic, Seasonal")
- S2
TX rhinoconjunctivitis or TX "rhino conjunctivitis"
- S3
TX "hay fever" or TX hayfever or TX pollinosis or TX pollenosis or TX sar or TX par or TX "pollen allergen*" or TX "season*allergic"
- S4
S1 or S2 or S3
- S5
(MH "Rhinitis")
- S6
TX Rhinitis
- S7
S5 or S6
- S8
TX intermittent* or TX season* or TX spring or TX summer or TX pollen* or TX grass* or TX birch or TX ragweed or TX tree* or TX weed* or TX mugwort or TX willow
- S9
TX alder or TX poaceae
- S10
S8 or S9
- S11
S7 and S10

S12
(MH "Desensitization, Immunologic")

S13
(MH "Allergens")

S14
TX desensiti* or hyposensiti*

S15
(MH "Immunotherapy")

S16
TX immunotherap* or TX immunomodulatory or TX "immune therapy" or TX "immunologic response*" or TX allergen* or TX antigen*

S17
TX grazax or TX pollinex or TX alutard

S18
s12 or s13 or s14 or s15 or s16 or s17

S19
s4 or s11

S20
s18 and s19
View Results (455)

S21
s18 and s19
Limiters - Clinical Queries: Therapy - Best Balance; Human
View Results (93)

Source – Science Citation Index (Web of Knowledge) 1900 – 2011

1
2,037
TS="seasonal allergic rhinitis

2
1,757
TS=rhinoconjunctivitis

3
95
TS="rhino conjunctivitis"

4
21,338
TS=(hayfever or pollinosis or pollenosis or sar)

5
7,479
TS=("hay fever" or "pollen allergen*" or "season* allergic")

6
29,405
#5 OR #4 OR #3 OR #2 OR #1

7
17,492
TS=rhinitis

8
>100,000

TS=(intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder or poaceae)

9
4,902
#8 AND #7

10
>100,000
TS=(allergen* or desensiti* or hyposensiti* or immunotherap* or immunomodulatory or antigen* or grazax or pollinex or alutard)

11
774
TS="immune therapy"

12
1,640
TS="immunologic response"

13
>100,000
#12 OR #11 OR #10

14
31,306
#9 OR #6

15
6,212
#14 AND #13

16
>100,000
TS=(trial OR random* OR control* OR placebo)

17
2,068
#15 AND #16

Indirect comparison methodology and results

Methods

Indirect comparison meta-analysis (ICMA) and indirect comparison meta-regression (ICMR)

Indirect comparison meta-analysis was conducted using methods outlined in Sutton (2000)¹ and Welton (2009)². As the outcomes (symptom scores, medication scores, combined symptom-medication scores) were measured using different scales, standardised score differences were pooled in the meta-analyses. The difference in effectiveness between SCIT and SLIT was estimated by subtracting one pooled standardised mean difference score (SLIT versus placebo) from the other pooled standardised mean difference score (SCIT versus placebo). A positive value indicates that the SLIT pooled score is higher than the SCIT pooled score (i.e. SCIT is a better treatment); a negative value indicates that SLIT is a better treatment.

Random effect modelling is a first step to account for unexplained heterogeneity (between study variability).¹ Possible sources of heterogeneity were also explored and adjusted for using meta-regression, with a number of trial, population, and reporting characteristics being used as covariates; specifically these comprised participant age (adult/paediatric), treatment duration, major allergen content of immunotherapy product and type of allergen (covariates as pre-specified in sub-group analyses in the Cochrane review). We also conducted a post-hoc exploration using year of publication as a covariate.

Parameter estimates were obtained via Bayesian modelling and Markov Chain Monte Carlo modelling.^{2,3,4} The software for Bayesian modelling WinBUGS 1.4⁵ was used to implement the models. The choice between random effect and fixed effect models and the significance of regression parameters when heterogeneity was explored by means of covariates was assessed by means of the Deviance Information Criteria (DIC).⁶ The DIC statistic is a compound measure of the model fit (the deviance) and the complexity of the model (the estimate of the effective number of parameters in the model). The lower the DIC the better the fit; for choosing between two models, a minimum difference of 5 in the DIC is recommended.⁷

When interpreting the pooled standardised score differences, the 95% credible intervals need to be considered⁸, with wider intervals indicating greater uncertainty. Probabilistic analyses were also undertaken and best estimate probabilities presented. These show the probability of either SLIT or SCIT being the best treatment; however, the probability does not give any information on how much better one treatment is likely to be (i.e. they are not a measures of effectiveness). Note that even where there is a very high probability of one treatment being best, the 95% credible intervals around the pooled standardised score differences may include zero and the results will therefore not be statistically significant.

Results

The following interpretation of results relating to symptom scores is given as an example. Subsequent results can be similarly interpreted.

Symptom scores

For every meta-analysis and meta-regression model, Table 1 presents estimates of parameters and the DIC (model fit statistic) for symptom scores. Probabilistic analysis is shown in Table 2 where, for every model, the probability of each treatment being the best treatment is given.

The fixed and random effect model for symptom scores included 59 studies. The DIC for the random effect model (508) is meaningfully lower than the DIC for the fixed effect model (542). The indirect comparison of SLIT versus SCIT is in favour of SCIT where the difference between scores is significantly positive (i.e. SCIT corresponds to lower symptom score (d_{32} 0.351 (0.127 to 0.586)). The probabilistic analysis also indicates that SCIT is the best treatment when symptoms scores are considered, with a probability associated with SCIT being the best treatment nearly equal to 100%. For every meta-analysis and meta-regression model, probabilistic analyses indicate that the probability of placebo being the best treatment is zero. The data reveals a substantial amount of unexplained heterogeneity (σ^2 0.089 (0.027 to 0.187)). Meta-regression results are presented separately for each covariate. For simplicity, since the fixed effects model corresponds to a much worse fit to the data than the random effects model, meta-regression will be based on the random effect model, and therefore the NULL model will refer to the random effects model without covariate effects.

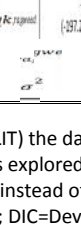
Age of participants (59 records). Age of participants did not improve model fit significantly with a difference of only 2 points in DIC (506) when compared to the NULL model. In fact, credible intervals for regression coefficients included the no-effect value of zero (β 0.455 (-0.434 to 1.358) and β 0.186 (-0.083 to 0.466)) and the between study variance remained largely unchanged compared to the random effect NULL model (σ^2 0.091 (0.028 to 0.192)). The probabilistic analysis indicates that there is a high probability that SCIT is the best treatment for adults (about 96%) reflecting a statistically significantly standardised mean difference score ($d_{32,adult}$ 0.328 (0.088 to 0.579)) in favour of SCIT. However, for studies that included only children this probability is almost even and the standardised mean difference was not significantly different from zero ($d_{32,child}$ 0.059 (-0.837 to 0.966)). This uncertainty may be explained by the fact that there is only one study comparing SCIT to placebo in children.

Year of Publication (59 records). Year of publication might be considered a source of differences between studies that depend on time, for example a proxy for technological or methodological advancements that are not explicitly considered. Year of publication as a covariate improves the fit of the model to the data compared to the NULL model (i.e. 6 points improvement of DIC, 502 compared

to 508). The between study variance is slightly lower than for the NULL model (σ^2 0.067 (0.017 to 0.147)). The probability of SCIT being the best treatment when year of publication is included in the model shifts over time to a probability of SLIT being the best treatment. This is reflected in Figure 1 (see main article), which shown the changing probabilities over time. Note that the standardised score differences at year 2005 and 2010 (Table 1) are not statistically significant, and the table is merely a reflection of the probability of one treatment being the best one, not of actual differences (significant or otherwise) of effectiveness. Being based on a post-hoc analysis and on one outcome measure only (symptom scores), this analysis should be considered exploratory in nature.

			SCIT vs Placebo	SLIT vs Placebo	SLIT vs SCIT	
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Model (covariate included in the model)	N	Parameter	SCIT vs Placebo Direct comparisons (k='2')	SLIT vs Placebo Direct comparisons (k='3')	SLIT vs SCIT Indirect comparison (k='32')	DIC (pD)
			Posterior mean (95% CrI)	Posterior mean (95% CrI)	Posterior mean (95% CrI)	
Random effect (Allergen type)	60 *		-0.326 (-0.868 to 0.204)	0.053 (-0.423 to 0.538)	-	523 (100) [525 (95)]
			0.196 (-0.291 to 0.699)	-0.108 (-0.438 to 0.223)	-	
			0.437 (-0.468 to 1.371)	-1.092 (-2.119 to -0.067)	-	
			0.276 (-196.40 to 197.30)	-0.109 (-0.562 to 0.346)	-	
			-0.721 (-1.013 to -0.451)	-0.326 (-0.473 to -0.185)	0.396 (0.090 to 0.721)	
			-1.047 (-1.532 to -0.599)	-0.272 (-0.728 to 0.188)	0.775 (0.140 to 1.446)	
			-0.526 (-0.941 to -0.121)	-0.433 (-0.735 to -0.138)	0.092 (-0.408 to 0.597)	
			-0.285 (-1.150 to 0.594)	-1.418 (-2.431 to -0.404)	-1.133 (-2.460 to 0.199)	
			-0.445 (-197.20 to 196.60)	-0.435 (-0.867 to -0.007)	0.011 (-197.0 to 196.70)	
			0.096 (0.030 to 0.20)			
			0.096 (0.030 to 0.20)			
			0.096 (0.030 to 0.20)			
			0.096 (0.030 to 0.20)			
			0.096 (0.030 to 0.20)			
			0.096 (0.030 to 0.20)			

*For Drachenberg (2001, SLIT) the data used were combined scores for allergen types, TREE and GRASS. However, when the effect of different allergen types was explored via meta-regression, separate scores for the two allergen types were used. Therefore, the number of studies in the analysis is 60 instead of 59.

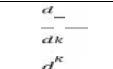
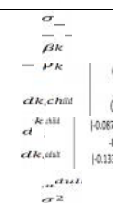
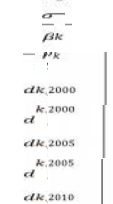
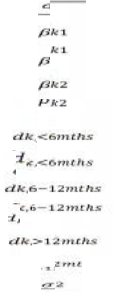
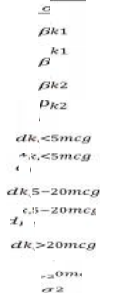
σ^2 =between study variance; DIC=Deviance Information Criteria; β =regression coefficient; d=standardised score difference

Table E2 Probabilistic analysis for symptom scores

Probability that SCIT or SLIT is the best treatment under different modelling assumptions				
		Placebo	SCIT	SLIT
Fixed effect (59)		00.0%	>99%	00.0%
Random effect (59)		00.0%	99.9%	00.1%
Age of participants (59)	Child	00.9%	54.9%	44.2%
	Adult	00.0%	99.6%	00.4%
Year of Publication (59)	2000	00.0%	99.9%	00.1%
	2005	00.0%	86.1%	13.9%
	2010	00.0%	20.3%	79.7%
Number of symptoms (48)	3 sym	00.0%	41.5%	58.5%
	6 sym	00.0%	96.5%	03.5%
	12 sym	00.0%	99.7%	00.3%
Duration	low	00.0%	>99%	00.0%
	med	00.0%	80.1%	19.9%
	high	00.0%	83.4%	16.6%
Major allergen content	<5 mcg	00.0%	47.4%	52.6%
	5-20mcg	00.0%	92.0%	08.0%
	>20mcg	00.0%	99.7%	00.3%
Allergen type	Grass	00.0%	99.4%	00.6%
	Parietaria	00.0%	99.1%	00.9%
	Tree	00.0%	64.3%	35.7%
	Alternaria	00.1%	04.6%	95.3%
	Ragweed	01.2%	50.0%	48.8%

*few studies on children compared SCIT vs Placebo and SLIT vs Placebo

Table E3 Standardised score differences (medication scores) for SCIT versus SLIT

Model (covariate included in the model)	N	Parameter	SCIT vs Placebo*** Direct comparisons (k=2')	SLIT vs Placebo*** Direct comparisons (k=3')	SLIT vs SCIT*** Indirect comparison (k=32')	DIC (pD)
			Posterior mean (95% CrI)	Posterior mean (95% CrI)	Posterior mean (95% CrI)	
Fixed effect (no covariates)	51		-0.469 (-0.592 to -0.347)	-0.220 (-0.283 to -0.158)	0.249 (0.111 to 0.386)	459 (53)
Random effect (no covariates) NULL MODEL	51		-0.579 (-0.808 to -0.370)	-0.306 (-0.449 to -0.177)	0.273 (0.027 to 0.529)	423 (83)
Random effect (Age of participants)	51		0.017 (-0.085 to 0.125) -0.051 (-0.087 to -0.019) -0.034 (-0.133 to 0.065)	-0.002 (-0.064 to 0.063) -0.041 (-0.069 to -0.017) -0.043 (-0.101 to 0.015)	- 0.009 (-0.031 to 0.050) -0.009 (-0.124 to 0.106)	429 (79)
Random effect (Year of Publication)	51		0.037 (-0.001 to 0.076) -0.661 (-0.899 to -0.437) -0.476 (-0.715 to -0.247) -0.291 (-0.650 to 0.067)	0.017 (-0.010 to 0.044) -0.388 (-0.576 to -0.208) -0.302 (-0.439 to -0.176) -0.217 (-0.416 to -0.029)	- 0.273 (-0.016 to 0.571) 0.174 (-0.091 to 0.439) 0.074 (-0.335 to 0.477)	422 (82)
Random effect (Duration**)	48		-0.111 (-0.894 to 0.671) -0.287 (-0.977 to 0.379) -0.395 (-0.994 to 0.202) -0.506 (-1.013 to -0.007) -0.682 (-1.010 to -0.375)	0.075 (-0.261 to 0.405) 0.219 (-0.142 to 0.589) -0.389 (-0.620 to -0.170) -0.314 (-0.573 to -0.073) -0.170 (-0.461 to 0.114)	- - 0.006 (-0.634 to 0.643) 0.192 (-0.376 to 0.750) 0.511 (0.094 to 0.950)	375 (81) [376 (77)]*
Random effect (Major allergen content)	37		-0.135 (-0.670 to 0.397) -0.231 (-0.853 to 0.371) -0.317 (-0.765 to 0.121) -0.452 (-0.754 to -0.153) -0.549 (-0.981 to -0.139)	0.434 (0.074 to 0.806) 0.352 (-0.035 to 0.740) -0.603 (-0.943 to -0.274) -0.169 (-0.319 to -0.016) -0.251 (-0.461 to -0.054)	- - -0.286 (-0.849 to 0.266) 0.283 (-0.049 to 0.622) 0.298 (-0.164 to 0.765)	243 (57) [243 (53)]*
Model (covariate included in the model)	N	Parameter	SCIT vs Placebo*** Direct comparisons (k=2')	SLIT vs Placebo*** Direct comparisons (k=3')	SLIT vs SCIT*** Indirect comparison (k=32')	DIC (pD)
			Posterior mean (95% CrI)	Posterior mean (95% CrI)	Posterior mean (95% CrI)	

Random effect (Allergen type)	52****	β_{R1}	0.276 (-0.317 to 0.915)	-0.297 (-0.776 to 0.184)	-	440 (87) [438 (83)]*	
		β	0.351	-0.199			
		β_{R2}	(-0.142 to 0.879)	(-0.540 to 0.143)	-		
		β	-0.114	-1.226			
		β_{R3}	(-1.061 to 0.855)	(-2.203 to -0.246)	-		
		β	0.125	-0.129			
		β_{R4}	(-0.896 to 1.152)	(-0.586 to 0.337)	-		
		β	-0.715	-0.211			
		dIC_{grass}	(-1.052 to -0.416)	(-0.383 to -0.050)	0.504 (0.169 to 0.873)		
		$dIC_{parietaria}$	(-0.967 to 0.092)	(-0.958 to -0.058)	-0.068 (-0.761 to 0.619)		
		dIC_{tree}	(-0.771 to 0.041)	(-0.712 to -0.114)	-0.045 (-0.550 to 0.453)		
		$dIC_{alternaria}$	(-1.734 to -0.067)	(-2.399 to -0.472)	-0.608 (-1.933 to 0.710)		
		$dIC_{ragweed}$	(-1.575 to 0.381)	(-0.771 to 0.095)	0.251 (-0.809 to 1.325)		
		σ^2	0.094 (0.024 to 0.209)				
		DIC					
		σ^2					

*For Drachenberg (2001, SLIT) the data used were combined scores for allergen types, TREE and GRASS. However, when the effect of different allergen types was explored via meta-regression, separate scores for the two allergen types were used. Therefore, the number of studies in the analysis is 60 instead of 59.

σ^2 =between study variance; DIC=Deviance Information Criteria; β =regression coefficient; d=standardised score difference

Table E4 Probabilistic analysis for medication scores

Probability that SCIT or SLIT is the best treatment under different modelling assumptions				
		Placebo	SCIT	SLIT
Fixed effect (51)		00.0%	>99%	00.0%
Random effect (51)		00.0%	98.4%	01.6%
Age of participants (51)	Child	00.0%	68.1%	31.9%
	Adult	01.8%	43.1%	55.1%
Year of Publication (51)	2000	00.0%	96.9%	03.1%
	2005	00.0%	90.6%	09.4%
	2010	00.1%	64.6%	35.3%
Duration (48)	low	00.0%	50.9%	49.1%
	med	00.0%	75.6%	24.3%
	high	00.0%	99.1%	00.9%
Major allergen content (37)	<5 mcg	00.0%	15.1%	84.9%
	5-20mcg	00.0%	95.3%	04.7%
	>20mcg	00.0%	90.4%	09.6%
Allergen type (52)	Grass	00.0%	99.8%	00.2%
	Parietaria	00.1%	42.1%	57.9%
	Tree	00.0%	43.0%	57.0%
	Alternaria	00.0%	18.0%	82.0%
	Ragweed	00.8%	67.8%	31.4%

Table E5 Standardised score differences (symptom-medication scores) for SCIT versus SLIT

Model (covariate included in the model)	N	Parameter	SCIT vs Placebo*** Direct comparisons (k='2')	SLIT vs Placebo*** Direct comparisons (k='3')	SLIT vs SCIT*** Indirect comparison (k='32')	DIC (pD)
			Posterior mean (95% CrI)	Posterior mean (95% CrI)	Posterior mean (95% CrI)	
Fixed effect (no covariates)	15	μ σ^2	-0.414 (-0.499 to -0.328)	-0.389 (-196.20 to 193.70)	0.024 (-195.80 to 194.10)	94 (16)
Random effect (no covariates) NULL MODEL	15	μ σ^2	-0.440 (-0.579 to -0.326)	-0.127 (-196.20 to 196.70) 0.017 (0.0 to 0.086)	0.313 (-195.80 to 197.10)	95 (20)
Random effect (Age of participants)	15	μ β_k σ^2 μ_{child} μ_{adult} σ^2	0.206 (-0.155 to 0.604) -0.258 (-0.616 to 0.097) -0.464 (-0.616 to -0.346)	-0.012 (-195.50 to 195.10) -0.170 (-277.60 to 274.30) -0.157 (-196.90 to 196.20)	- 0.089 (-277.30 to 274.70) 0.307 (-196.40 to 196.70)	95 (20)
Random effect (Year of Publication)	15	μ β_k σ^2 μ_{2000} μ_{2005} μ_{2010} σ^2	0.010 (-0.011 to 0.032) -0.513 (-0.716 to -0.331) -0.461 (-0.605 to -0.338) -0.409 (-0.566 to -0.276)	0.337 (-195.60 to 196.40) -1.606 (-1005.0 to 994.80) 0.079 (-196.30 to 195.80) 1.764 (-998.50 to 1003.0)	- -1.093 (-1004.0 to 995.30) 0.540 (-195.80 to 196.20) 2.173 (-998.10 to 1003.0)	96 (21)
Random effect (Duration)	12	μ β_{k1} β β_{k2} σ^2 $\mu_{<6mths}$ $\mu_{6-12mths}$ $\mu_{>12mths}$ σ^2	-0.016 (-0.544 to 0.387) -0.106 (-0.427 to 0.253) -0.387 (-0.668 to -0.160) -0.404 (-0.915 to -0.079) -0.494 (-0.736 to -0.272)	-0.109 (-195.40 to 195.40) 0.092 (-196.0 to 195.10) 0.288 (-196.10 to 197.70) 0.180 (-275.0 to 279.10) 0.380 (-276.60 to 278.70)	- - 0.676 (-195.70 to 198.10) 0.583 (-274.60 to 279.40) 0.874 (-276.10 to 279.20)	97 (18) [95 (17)]
Random effect (Major allergen content)	10	μ β_{k1} β β_{k2} σ^2 $\mu_{<5mcg}$ $\mu_{5-20mcg}$ $\mu_{>20mcg}$ σ^2	0.169 (-0.257 to 0.668) -0.244 (-0.855 to 0.403) -0.508 (-0.911 to -0.180) -0.340 (-0.638 to -0.061) -0.753 (-1.285 to -0.251)	-0.189 (-196.60 to 194.90) 0.094 (-195.0 to 196.40) -0.004 (-197.40 to 197.90) -0.192 (-278.30 to 277.40) 0.091 (-277.10 to 280.20)	- - 0.505 (-196.90 to 198.40) 0.148 (-278.0 to 277.80) 0.843 (-276.50 to 280.90)	75 (16) [75 (15)]

Model (covariate included in the model)	N	Parameter	SCIT vs Placebo*** Direct comparisons (k=2')	SLIT vs Placebo*** Direct comparisons (k=3')	SLIT vs SCIT*** Indirect comparison (k=32')	DIC (pD)
			Posterior mean (95% CrI)	Posterior mean (95% CrI)	Posterior mean (95% CrI)	
Random effect (Allergen type)	15	β_{k1}	-0.586 (-1.075 to -0.109)	0.359 (-194.90 to 197.30)	-	93 (22)
		β_{k2}	0.028 (-0.321 to 0.371)	0.039 (-196.40 to 198.10)	-	
		β_{k3}	-0.847 (-1.655 to -0.040)	-0.129 (-195.70 to 195.70)	-	
		β_{k4}	-0.149 (-0.679 to 0.374)	0.418 (-195.10 to 194.60)	-	
		β_{k5}	-0.387 (-0.512 to -0.269)	0.236 (-195.30 to 195.40)	0.623 (-194.90 to 195.70)	
		β_{k6}	-0.973 (-1.447 to -0.509)	0.595 (-276.60 to 276.20)	1.568 (-275.70 to 277.10)	
		β_{k7}	-0.359 (-0.688 to -0.042)	0.274 (-278.10 to 277.80)	0.633 (-277.90 to 278.20)	
		β_{k8}	-1.234 (-2.035 to -0.439)	0.107 (-275.90 to 277.50)	1.341 (-274.70 to 278.70)	
		β_{k9}	-0.536 (-1.059 to -0.028)	0.654 (-279.10 to 277.90)	1.189 (-278.60 to 278.40)	
		β_{k10}		0.011 (0.0 to 0.059)		
		β_{k11}				
		β_{k12}				
		β_{k13}				
		β_{k14}				
		β_{k15}				

σ^2 =between study variance; DIC=Deviance Information Criteria; β =regression coefficient; d=standardised score difference

Table E6 Probabilistic analysis for symptom-medication scores

Probability that SCIT or SLIT is the best treatment under different modelling assumptions				
		Placebo	SCIT	SLIT
Fixed effect (15)		00.0%	50.2%	49.8%
Random effect (15)		00.0%	50.2%	49.8%
Age of participants (15)	Child	02.9%	47.1%	50.0%
	Adult	00.0%	50.2%	49.8%
Year of Publication (15)	2000	00.0%	49.8%	50.2%
	2005	00.0%	50.4%	49.7%
	2010	00.0%	50.3%	49.7%
Duration (12)	low	00.1%	50.2%	49.7%
	med	00.5%	49.8%	49.8%
	high	00.0%	50.4%	49.6%
Major allergen content (10)	<5 mcg	00.2%	50.0%	49.9%
	5-20mcg	00.7%	49.2%	50.0%
	>20mcg	00.2%	49.8%	50.0%
Allergen type (15)	Grass	00.0%	50.3%	49.7%
	Parietaria	00.0%	50.4%	49.6%
	Tree	00.7%	49.5%	49.8%
	Alternaria	00.1%	50.3%	49.7%
	Ragweed	01.0%	49.5%	49.5%

Table E7 Standardised score differences (quality-of-life scores) for SCIT versus SLIT

Model (covariate included in the model)	N	Parameter	SCIT vs Placebo*** Direct comparisons (k=2')	SLIT vs Placebo*** Direct comparisons (k=3')	SLIT vs SCIT*** Indirect comparison (k=32')	DIC (pD)
			Posterior mean (95% CrI)	Posterior mean (95% CrI)	Posterior mean (95% CrI)	
Fixed effect (no covariates)	15	μ	-0.532 (-0.658 to -0.405)	-0.146 (-0.236 to -0.056)	0.386 (0.231 to 0.541)	43 (17)
Random effect (no covariates) NULL MODEL	15	σ^2	-0.580 (-0.892 to -0.280)	-0.197 (-0.498 to 0.089)	0.383 (-0.042 to 0.804)	-6 (27)
Random effect (Age of participants)	15	σ^2	0.119 (-196.0 to 196.40)	-0.122 (-0.996 to 0.779)	-	-6 (27)
		β_{age}	-0.465 (-196.50 to 195.90)	-0.304 (-1.117 to 0.518)	0.161 (-196.0 to 196.40)	
		β_{age}^2	-0.584 (-0.911 to -0.270)	-0.182 (-0.530 to 0.147)	0.402 (-0.062 to 0.864)	
		σ^2		0.149 (0.043 to 0.402)		
Random effect (Year of Publication)	15	σ^2	-0.014 (-0.218 to 0.188)	0.039 (-0.170 to 0.267)	-	-5 (28)
		β_{year}	-0.510 (-1.620 to 0.602)	-0.582 (-2.834 to 1.481)	-0.072 (-2.585 to 2.256)	
		β_{year}^2	-0.581 (-0.926 to -0.247)	-0.387 (-1.525 to 0.659)	0.194 (-0.986 to 1.30)	
		β_{year}^3	-0.651 (-1.691 to 0.364)	-0.193 (-0.532 to 0.137)	0.459 (-0.620 to 1.554)	
		σ^2		0.168 (0.048 to 0.467)		
Random effect (Duration)	15	σ^2	0.462 (-1.082 to 2.002)	-0.085 (-1.087 to 0.975)	-	-4 (28)
		$\beta_{duration}$	0.571 (-0.745 to 1.869)	-0.260 (-1.048 to 0.576)	-	
		$\beta_{duration}^2$	-1.096 (-2.327 to 0.146)	-0.113 (-0.616 to 0.343)	0.983 (-0.363 to 2.288)	
		$\beta_{duration}^3$	-0.634 (-1.562 to 0.297)	-0.198 (-1.113 to 0.719)	0.436 (-0.872 to 1.742)	
		$\beta_{duration}^4$	-0.525 (-0.936 to -0.120)	-0.373 (-1.027 to 0.280)	0.152 (-0.617 to 0.925)	
		σ^2		0.197 (0.045 to 0.612)		
Random effect (Major allergen content)	10	σ^2	-0.062 (-1.441 to 1.261)	-36.910 (-135.70 to 60.710)	-	1 (23)
		$\beta_{allergen}$	-0.068 (-1.418 to 1.279)	-36.570 (-135.30 to 61.020)	-	[-3 (18)]
		$\beta_{allergen}^2$	-0.587 (-1.767 to 0.593)	36.640 (-60.920 to 135.40)	37.220 (-60.470 to 136.0)	
		$\beta_{allergen}^3$	-0.649 (-1.354 to -0.007)	-0.274 (-0.889 to 0.332)	0.375 (-0.508 to 1.315)	
		$\beta_{allergen}^4$	-0.655 (-1.303 to -0.008)	0.063 (-0.820 to 0.782)	0.718 (-0.393 to 1.670)	
		σ^2		0.260 (0.015 to 1.0)		
Random effect (Allergen type)	15	σ^2	-0.159 (-0.899 to 0.585)	0.104 (-195.30 to 194.80)*	-	-5 (28)
		$\beta_{allergen_type}$	0.393 (-195.20 to 196.20)*	-0.816 (-1.849 to 0.223)	-	
		$\beta_{allergen_type}^2$	0.460 (-196.20 to 195.10)*	-0.157 (-195.20 to 194.0)*	-	
		$\beta_{allergen_type}^3$	-0.629 (-1.853 to 0.591)	-0.030 (-195.50 to 197.20)*	-	
		$\beta_{allergen_type}^4$	-0.304 (-1.319 to 0.723)	-0.017 (-195.80 to 195.90)*	-	
		$\beta_{allergen_type}^5$	-0.461 (-0.891 to -0.037)	-0.127 (-0.445 to 0.196)	0.334 (-0.197 to 0.868)	
		$\beta_{allergen_type}^6$	-0.620 (-1.224 to -0.009)	-0.022 (-195.40 to 194.80)	0.597 (-194.80 to 195.30)	
		$\beta_{allergen_type}^7$	-0.068 (-195.80 to 195.80)	-0.943 (-1.926 to 0.046)	-0.875 (-196.70 to 194.80)	
		$\beta_{allergen_type}^8$	-0.001 (-196.70 to 194.70)	-0.284 (-195.30 to 193.80)	-0.283 (-275.80 to 277.0)	
		$\beta_{allergen_type}^9$	-1.090 (-2.237 to 0.050)	-0.157 (-195.60 to 197.10)	0.933 (-194.70 to 198.0)	
		$\beta_{allergen_type}^{10}$	-0.765 (-1.696 to 0.164)	-0.143 (-195.90 to 195.80)	0.622 (-195.10 to 196.60)	
		σ^2		0.143 (0.038 to 0.420)		

*such a wide credible interval is due to the fact that there is not study reporting such covariate that can inform that parameter

Table E8 Probabilistic analysis for QoL scores

Probability that SCIT or SLIT is the best treatment under different modelling assumptions				
		Placebo	SCIT	SLIT
Fixed effect (15)		00.0%	>99%	00.0%
Random effect (15)		00.0%	96.4%	03.6%
Age of participants (15)	Child	10.5%	50.0%	39.5%
	Adult	00.0%	95.9%	04.1%
Year of Publication (15)	2000	05.0%	45.0%	49.9%
	2005	00.0%	64.5%	35.5%
	2010	01.2%	81.0%	17.8%
Duration (15)	low	01.3%	92.6%	06.1%
	med	02.6%	76.1%	21.3%
	high	00.2%	66.8%	33.0%
Major allergen content (10)	<5 mcg	10.9%	68.3%	20.9%
	5-20mcg	00.6%	83.3%	16.2%
	>20mcg	01.2%	91.3%	07.5%
Allergen type (15)	Grass	00.5%	90.2%	09.3%
	Parietaria	01.2%	49.1%	49.8%
	Tree	01.5%	49.7%	48.8%
	Alternaria	25.0%	37.4%	37.6%
	Ragweed	01.5%	48.9%	49.6%
	Sal k1	02.5%	47.8%	49.7%

RQLQ scores						
Covariate (No studies)	N	Parameter	SCIT vs Placebo	SLIT vs Placebo	SLIT vs SCIT (Indirect comparison)	DIC (pD)
Fixed effect	12	μ σ^2	-0.740 (-0.920 to -0.560)	0.071 (-0.010 to 0.151)	0.811 (0.614 to 1.007)	49 (14)
Random effect	12	μ σ^2	-0.764 (-1.116 to -0.425)	-0.247 (-0.729 to 0.156)	0.517 (-0.071 to 1.045)	-2 (26)
Random effect (Age of participants)	12	μ σ^2 β_{age} σ^2_{age} μ_{age} σ^2_{age} μ_{age} σ^2_{age} μ_{age} σ^2_{age} μ_{age} σ^2_{age}	-0.023 (-195.20 to 195.40) -0.788 (-196.10 to 194.60) -0.765 (-1.115 to -0.421)	-0.047 (-196.70 to 195.80) -0.294 (-197.10 to 195.60) -0.248 (-0.734 to 0.159)	- 0.493 (-276.90 to 278.70) 0.517 (-0.085 to 1.051)	-2 (21)
Random effect (Year of Publication)	12	μ σ^2 β_{year} σ^2_{year} μ_{year} σ^2_{year} μ_{year} σ^2_{year} μ_{year} σ^2_{year} μ_{year} σ^2_{year}	-0.034 (-0.280 to 0.216) -0.588 (-1.962 to 0.763) -0.758 (-1.162 to -0.370) -0.928 (-2.154 to 0.306)	0.133 (-0.169 to 0.475) -1.526 (-4.797 to 1.357) -0.860 (-2.466 to 0.558) -0.193 (-0.756 to 0.338)	- -0.939 (-4.488 to 2.230) -0.102 (-1.748 to 1.365) 0.735 (-0.634 to 2.074)	-1 (22)
Random effect (Duration)	12	μ σ^2 $\beta_{duration}$ $\sigma^2_{duration}$ $\mu_{duration}$ $\sigma^2_{duration}$ $\mu_{duration}$ $\sigma^2_{duration}$ $\mu_{duration}$ $\sigma^2_{duration}$ $\mu_{duration}$ $\sigma^2_{duration}$	0.202 (-1.426 to 1.853) 0.393 (-0.986 to 1.763) -1.094 (-2.395 to 0.206) -0.892 (-1.909 to 0.138) -0.70 (-1.170 to -0.251)	-0.212 (-195.10 to 194.80) -0.182 (-1.092 to 1.039) -0.144 (-1.107 to 0.518) -0.355 (-195.20 to 194.60) -0.326 (-1.034 to 0.388)	- - 0.950 (-0.686 to 2.364) 0.536 (-194.30 to 195.20) 0.374 (-0.454 to 1.228)	1 (22)
Random effect (Major allergen content)	10	μ σ^2 $\beta_{allergen}$ $\sigma^2_{allergen}$ $\mu_{allergen}$ $\sigma^2_{allergen}$ $\mu_{allergen}$ $\sigma^2_{allergen}$ $\mu_{allergen}$ $\sigma^2_{allergen}$	-0.309 (-138.70 to 137.60) -0.230 (-196.80 to 195.50) -0.546 (-138.40 to 137.90) -0.855 (-1.237 to -0.475) -0.775 (-239.60 to 240.10)	0.008 (-138.50 to 139.60) 0.411 (-195.60 to 197.40) -0.171 (-139.80 to 138.30) -0.162 (-0.782 to 0.303) 0.240 (-238.80 to 240.70)	- - 0.375 (-195.10 to 196.20) 0.692 (-0.046 to 1.281) 1.015 (-337.90 to 341.10)	4 (19) [1 (17)]
Random effect (allergen type)	12	μ σ^2 $\beta_{allergen}$ $\sigma^2_{allergen}$ $\mu_{allergen}$ $\sigma^2_{allergen}$ $\mu_{allergen}$ $\sigma^2_{allergen}$ $\mu_{allergen}$ $\sigma^2_{allergen}$ $\mu_{allergen}$ $\sigma^2_{allergen}$	-0.121 (-0.987 to 0.780) -0.128 (-195.90 to 195.90) 0.014 (-194.60 to 195.0) -0.416 (-1.741 to 0.937) -0.117 (-1.276 to 1.059) -0.685 (-1.213 to -0.171) -0.806 (-1.511 to -0.081) -0.813 (-196.60 to 195.20) -0.671 (-195.50 to 194.40) -1.101 (-2.327 to 0.144) -0.802 (-1.858 to 0.251)	0.710 (-195.20 to 196.10) -1.222 (-2.588 to 0.152) 0.439 (-196.60 to 196.40) -0.140 (-195.50 to 194.70) -0.253 (-196.50 to 194.30) -0.109 (-0.637 to 0.411) 0.602 (-195.40 to 195.90) -1.330 (-2.597 to -0.062) 0.330 (-196.70 to 196.40) -0.249 (-195.70 to 194.70) -0.361 (-196.60 to 194.30)	0.576 (-0.154 to 1.316) 1.407 (-194.60 to 196.60) -0.518 (-196.60 to 195.30) 1.001 (-276.20 to 276.10) 0.852 (-194.50 to 195.50) 0.440 (-195.70 to 195.20)	-1 (22)

σ^2 =between study variance; DIC=Deviance Information Criteria; β =regression coefficient; d=standardised score difference

Table E10 Probabilistic analysis for RQLQ scores

Probability that SCIT or SLIT is the best treatment under different modelling assumptions		Placebo	SCIT	SLIT
Fixed effect (12)		00.0%	>99%	00.0%
Random effect (12)		00.0%	96.2%	03.8%
Age of participants (12)	Child	24.7%	37.8%	37.5%
	Adult	00.0%	96.0%	04.0%
Year of Publication (12)	2000	02.8%	26.9%	70.3%
	2005	00.0%	46.3%	53.7%
	2010	01.5%	86.8%	11.8%
Duration (12)	low	01.5%	88.9%	09.6%
	med	01.9%	48.3%	49.8%
	high	00.1%	85.8%	14.0%
Major allergen content (10)	<5 mcg	24.9%	37.7%	37.4%
	5-20mcg	00.0%	97.0%	03.0%
	>20mcg	24.8%	37.7%	37.5%
Allergen type (12)	Grass	00.3%	94.7%	04.9%
	Parietaria	00.9%	49.6%	49.5%
	Tree	01.0%	49.7%	49.3%
	Alternaria	24.8%	37.9%	37.3%
	Ragweed	01.9%	48.4%	49.7%
	Sal k1	03.0%	47.3%	49.8%

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Figure Legends online repository meta-analyses

Figure E1 SCIT versus placebo: symptom scores

Figure E2 SCIT versus placebo: medication scores

Figure E3 SCIT versus placebo: symptom-medication scores

Figure E4 SCIT versus placebo: quality of life

Figure E5 SLIT versus placebo: symptom scores

Figure E6 SLIT versus placebo: medication scores

Figure E7 SLIT versus placebo: symptom-medication scores

Figure E8 SLIT versus placebo: quality of life

