Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method

Calamita Z, Saconato H, Pela A B, Atallah A N

CRD summary
This review concluded that sublingual immunotherapy demonstrated a small benefit for the treatment of asthma and that it is a safe alternative to subcutaneous immunotherapy, but further research is required. This was a reasonably well-conducted review and the authors’ cautious conclusion reflects the data presented.

Authors’ objectives
To determine the efficacy and safety of sublingual immunotherapy (SLIT) for asthma.

Searching
MEDLINE (1966 to 2005), EMBASE (1974 to 2005), LILACS (1982 to 2005) and the Cochrane Controlled Trials Register were searched, using a search filter for randomised controlled trials (RCTs); the search terms were reported. The reference lists of relevant studies were also checked. Non-English language publications were considered if the translated abstract or title indicated that the study was a relevant RCT.

Study selection
RCTs of immunotherapy delivered by sublingual route, with or without subsequent swallowing, were eligible for inclusion. The majority of the included studies were randomised-controlled, double-blind clinical trials; 6 trials were randomised-controlled, open clinical trials. All types of allergen, doses and lengths of treatment duration were allowed. A variety of allergens was administered, including mites, pollen, a mixture of allergens and latex. Extracts were mostly administered by drops, with the participant fasting; the drops were kept under the tongue for 1 to 3 minutes before swallowing. In all studies the comparator of interest was placebo. The duration of treatment ranged from 3 months to 3 years. The authors did not report specific criteria for the types of participants. The included participants had asthma, rhinitis and/or conjunctivitis. The severity of asthma was generally mild to moderate. Ten studies included only paediatric participants. Studies that reported asthmatic symptoms, asthmatic medication requirement, respiratory function tests, non-specific bronchial provocation and adverse events were eligible for inclusion.

Two reviewers independently selected studies for inclusion in the review, and any disagreements were resolved by consensus.

Assessment of study quality
The included studies were evaluated using Cochrane Handbook methods (i.e. allocation concealment) and the Jadad scale. One reviewer assessed the quality of the studies and a second checked the assessment.

Data extraction
The data were extracted directly into RevMan and study authors were contacted for further information where necessary. Continuous outcomes (asthma symptoms, allergic symptoms, symptoms plus medication, medication use, and respiratory function and bronchial provocation tests) were calculated as the standard mean difference (SMD), while categorical outcomes (asthma improvements in general and adverse events) were calculated as the risk difference (RD) or relative risk (RR) along with the 95% confidence interval (CI). The number-needed-to-treat (NNT) was also calculated. Results were analysed as intention-to-treat for the categorical data and by the number of participants that completed the trial for continuous data.

One reviewer extracted the data and a second checked the extraction. Any disagreements were resolved through consensus.

Methods of synthesis
The studies were combined in a meta-analysis using a random-effects model, grouped by outcome. Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ tests ($p<0.01$ indicated a significant difference). A sensitivity analysis that looked at study quality was performed.

Results of the review

Twenty-five RCTs ($n=1,706$) were included in the review: 19 were randomised-controlled, double-blind clinical trials and 6 randomised-controlled, open clinical trials.

Adequate allocation concealment was reported in 12 studies. The Jadad quality score ranged from 2 to 5 (12 RCTs scored 5, four scored 4, seven scored 3 and two scored 2).

Asthma improvements in general (7 RCTs, $n=876$): compared with placebo, SLIT was found to significantly reduce asthma severity (RD -0.27, 95% CI: -0.33, -0.21 and RR 0.48, 95% CI: 0.40, 0.57). There was no evidence of significant statistical heterogeneity. The NNT using immunotherapy to avoid leaving one patient with no improvement or worse symptoms was 3.70 patients.

Adverse effects (20 RCTs, $n=1,501$): compared with placebo, a significant likelihood of adverse effects with SLIT was found (RD 0.07, 95% CI: 0.04, 0.10 and RR 1.83, 95% CI: 1.40, 2.40). There was no evidence of significant statistical heterogeneity. The NNT using SLIT was 14.28 patients. No severe adverse effects were reported. Reported mild adverse events included local reactions such as pruritis, erythema and oedema, which usually occurred within 30 minutes of treatment and generally resolved spontaneously.

Asthma symptoms (9 RCTs, $n=303$): a non significant reduction in symptoms was found (SMD -0.38, 95% CI: -0.79, 0.03). However, there was evidence of significant statistical heterogeneity. The sensitivity analysis did not significantly alter the results.

Allergic symptoms in general (10 RCTs, $n=360$): a significant reduction in allergic symptoms was found (SMD -1.18, 95% CI: -1.93, -0.43). However, there was evidence of significant statistical heterogeneity. The sensitivity analysis did not significantly alter the results.

Composite symptom plus medication scores (7 RCTs, $n=724$): when analysing outcomes for asthma together with rhinitis and conjunctivitis, a significant difference in favour of SLIT was found (SMD -0.79, 95% CI: -1.34, -0.24). However, there was evidence of significant statistical heterogeneity. Only one study looked at asthma alone, which reported that no significant between group differences were found.

Medication use: a significant reduction in the use of medication for asthma, rhinitis and conjunctivitis was found in favour of SLIT (SMD -0.82, 95% CI: -1.25, -0.39), based on 10 RCTs ($n=488$). However, no significant difference was found in the use of medication for asthma alone (SMD -0.91, 95% CI: -1.94, 0.12), based on 6 RCTs ($n=254$). There was evidence of significant statistical heterogeneity for both outcomes.

Respiratory function and bronchial provocation tests: significant improvements in favour of SLIT were found on the respiratory function test FEV1% (SMD 1.48, 95% CI: 0.13, 2.82), based on 4 RCTs ($n=144$), and on the FEF25-75% (SMD 1.06, 95% CI: 0.40, 1.72), based on 2 studies ($n=42$). No significant between-group differences were found on any of the other tests in this category.

Authors’ conclusions

SLIT demonstrated a small benefit for the treatment of asthma and is a safe alternative to subcutaneous-specific immunotherapy, but further good quality research is needed.

CRD commentary

The review question was supported by clear inclusion criteria relating to the study design, intervention and outcomes. Several sources were searched in order to locate relevant papers. The search was not restricted by language, thus minimising the likelihood of language bias. However, the authors do not appear to have made any attempt to locate unpublished material, thereby increasing the possibility of publication bias. Methods undertaken to select studies for the review, assess study validity and extract the data were likely to have minimised the possibility of error or bias, and the
methodological quality of the included studies was clearly reported. The studies were combined using standardised meta-analytic methods and statistical heterogeneity was assessed. In addition, the authors attempted to evaluate a possible cause of heterogeneity. This was a reasonably well-conducted study and the authors’ cautious conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors suggested that SLIT is a safe alternative to subcutaneous immunotherapy.

**Research:** The authors stated that further RCTs with standardised symptom scores and medications are needed to verify these findings and to determine the optimal maintenance doses and length of treatment. RCTs also need to determine whether particular patient groups respond better than others. The authors also recommended research to determine the cost-effectiveness ratio and levels of adherence to treatment.

**Funding**

Not stated.

**Bibliographic details**


**PubMedID**

16942563

**DOI**

10.1111/j.1398-9995.2006.01205.x

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Administration, Sublingual; Adolescent; Adult; Asthma /immunology /therapy; Child; Data Interpretation, Statistical; Desensitization, Immunologic /adverse effects; Humans; Immunotherapy; Randomized Controlled Trials as Topic

**AccessionNumber**

12006007120

**Date bibliographic record published**

10/03/2008

**Date abstract record published**

01/09/2008

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.