

Is sublingual immunotherapy for asthma effective and safe?

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Asthma is characterized by chronic airway inflammation and strongly associated with specific allergy to inhalants.^{1,2} Sublingual Immunotherapy (SLIT) induces desensitization and immune tolerance to specific allergens including inhalants, so may be useful for treating asthma. The role of SLIT in management of asthma is not, however, clearly established.² This Cochrane Corner aims to summarize the effectiveness and safety of SLIT for asthma treatment.

1 | COCHRANE ABSTRACT: SUBLINGUAL IMMUNOTHERAPY FOR ASTHMA

1.1 | Disclaimer

This is an abstract of a Cochrane Review "Sublingual Immunotherapy for Asthma" published in Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD011293. 10.1002/14651858.CD011293.pub3. Accessed 08 Aug 2021.³ (see www.cochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Library should be consulted for the most recent version of the review.

1.2 | Background

Asthma is a common long-term respiratory disease affecting approximately 300 million people worldwide. Approximately half of people with asthma have an important allergic component to their disease, which may provide an opportunity for targeted treatment. Sublingual immunotherapy (SLIT) aims to reduce asthma symptoms by delivering increasing doses of an allergen (eg house dust mite, pollen extract) under the tongue to induce immune tolerance. Fifty-two studies were identified and synthesized in the original Cochrane Review in 2015, but questions remained about the safety and efficacy of sublingual immunotherapy for people with asthma.

1.3 | Objectives

To assess the efficacy and safety of sublingual immunotherapy compared with placebo or standard care for adults and children with asthma.

1.4 | Search methods

The original searches for trials from the Cochrane Airways Group Specialised Register (CAGR), ClinicalTrials.gov, WHO ICTRP and reference lists of all primary studies and review articles found trials up to 25 March 2015. The most recent search for trials for the current update was conducted on 29 October 2019.

1.5 | Selection criteria

We included parallel randomized controlled trials, irrespective of blinding or duration, that evaluated sublingual immunotherapy versus placebo or as an add-on to standard asthma management. We included both adults and children with asthma of any severity and with any allergen-sensitization pattern. We included studies that recruited participants with asthma, rhinitis or both, providing at least 80% of trial participants had a diagnosis of asthma. We selected outcomes to reflect recommended outcomes for asthma clinical trials and those most important to people with asthma. Primary outcomes were asthma exacerbations requiring a visit to the emergency department (ED) or admission to hospital, validated measures of quality of life and all-cause serious adverse events (SAEs). Secondary outcomes were asthma symptom scores, exacerbations requiring systemic corticosteroids, response to provocation tests and dose of inhaled corticosteroids (ICS).

1.6 | Data collection and analysis

Two review authors independently screened the search results for included trials, extracted numerical data and assessed risk of bias,

all of which were cross-checked for accuracy. Any disagreements were resolved by discussion. We analysed dichotomous data as odds ratios (ORs) or risk differences (RDs) using study participants as the unit of analysis; we analysed continuous data as mean differences (MDs) or standardized mean differences (SMDs) using random-effects models. We considered the strength of evidence for all primary and secondary outcomes using the GRADE approach.

1.7 | Main results

Sixty-six studies met the inclusion criteria for this update, including 52 studies from the original review. Most studies were double-blind and placebo-controlled, varied in duration from one day to three years, and recruited participants with mild or intermittent asthma, often with comorbid allergic rhinitis. Twenty-three studies recruited adults and teenagers; 31 recruited only children; three recruited both; and nine did not specify. The pattern of reports and results remained largely unchanged from the original review despite 14 further studies and a 50% increase in participants studied (5077–7944).

Reporting of primary efficacy outcomes to measure the impact of SLIT on asthma exacerbations and quality of life was infrequent, and selective reporting may have had a serious effect on the completeness of the evidence; 16 studies did not contribute any data, and a further six studies could only be included in a post hoc analysis of all adverse events. Allocation procedures were generally not well described; about a quarter of the studies were at high risk of performance or detection bias (or both); and participant attrition was high or unknown in around half of the studies.

The primary outcome in most studies did not align with those of interest to the review (mostly asthma or rhinitis symptoms), and only two small studies reported our primary outcome of exacerbations requiring an ED or hospital visit; the pooled estimate from these studies suggests SLIT may reduce exacerbations compared with placebo or usual care, but the evidence is very uncertain (OR 0.35, 95% confidence interval (CI) 0.10 to 1.20; $n = 108$; very low-certainty evidence).

Nine studies reporting quality of life could not be combined in a meta-analysis and, whilst the direction of effect mostly favoured SLIT, the effects were often uncertain and small.

SLIT likely does not increase SAEs compared with placebo or usual care, and analysis by risk difference suggests no more than 1 in 100 people taking SLIT will have a serious adverse event (RD -0.0004 , 95% CI -0.0072 to 0.0064 ; participants = 4810; studies = 29; moderate-certainty evidence).

Regarding secondary outcomes, asthma symptom and medication scores were mostly measured with non-validated scales, which precluded meaningful meta-analysis or interpretation, but there was a general trend of SLIT benefit over placebo. Changes in ICS use (MD -17.13 $\mu\text{g/d}$, 95% CI -61.19 to 26.93 ; low-certainty evidence), exacerbations requiring oral steroids (studies = 2; no events) and bronchial provocation (SMD 0.99 , 95% CI 0.17 to 1.82 ; low-certainty evidence) were not often reported. Results were imprecise and

Key messages

- Evidence for the effectiveness of sublingual immunotherapy for treating asthma is currently insufficient.
- Sublingual immunotherapy appears safe when used to treat other conditions in mild-to-moderate, well-controlled asthma
- Further work is needed to understand sublingual immunotherapy safety in severe and/or uncontrolled asthma.

included the possibility of important benefit or little effect and, in some cases, potential harm from SLIT.

More people taking SLIT had adverse events of any kind compared with control (OR 1.99, 95% CI 1.49 to 2.67; high-certainty evidence; participants = 4251; studies = 27), but events were usually reported to be transient and mild. Lack of data prevented most of the planned subgroup and sensitivity analyses.

1.8 | Authors' conclusions

Despite continued study in the field, the evidence for important outcomes such as exacerbations and quality of life remains too limited to draw clinically useful conclusions about the efficacy of SLIT for people with asthma. Trials mostly recruited mixed populations with mild and intermittent asthma and/or rhinitis and focussed on non-validated symptom and medication scores. The review findings suggest that SLIT may be a safe option for people with well-controlled mild-to-moderate asthma and rhinitis who are likely to be at low risk of serious harm, but the role of SLIT for people with uncontrolled asthma requires further evaluation.

2 | COMMENTARY

Asthma is a common chronic disease and an important cause of morbidity and mortality.² Specific allergies play a significant role in asthma pathogenesis, so assessing the role of SLIT in asthma management is relevant.⁴ It is therefore disappointing that this updated Cochrane review, which includes 66 clinical trials in almost 8000 children and adults with asthma, concludes yet again that “more research is needed.” We might ask how 66 separate clinical trials fail to reach a robust conclusion; it is not because Cochrane is being unusually cautious. The findings are consistent with current guidance that SLIT is not recommended for treatment of asthma alone.^{2,4}

A key explanation for the inconclusive findings is that trials failed to use a consistent set of outcome measures which were relevant to people with asthma, their carers or healthcare professionals. There was insufficient information about asthma exacerbations or medication use, which represent key economic burdens. There was some information about quality of life, generally in a favourable direction,

but often using non-validated scores, with diverse outcome measures precluding meta-analysis. This Cochrane review supports the need for core outcome measurement development in asthma, something that has been championed across chronic diseases, for example OMERACT in rheumatoid arthritis.⁵ The use of core outcome sets in future clinical studies would allow for more meaningful meta-analyses and increased confidence in the benefit or lack of benefit for SLIT.⁶

The review suggested that SLIT causes only minor adverse effects so is reassuring about the safety of SLIT for treating mild-to-moderate asthma.

The review did not evaluate cost-effectiveness of SLIT. Grass pollen SLIT (Grazax ALK-Abelló) costs ~£821/year⁷ and HDM SLIT costs ~£1359/year.⁸ This is significant, although for some patients will be less than pharmacological treatments, which have a stronger efficacy but a more concerning safety profile than SLIT.⁹

More work needs to be undertaken before SLIT can be recommended for patients with asthma, but in patients where SLIT is being considered for treating other conditions, these Cochrane review findings reassure us that well-controlled mild or moderate asthma should not be considered a contraindication to commencing SLIT treatment.

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CONFLICTS OF INTEREST

Dr Fulmali and Dr Kimkool have no conflicts of interest to declare.

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