Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies

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Authors' objectives
To compare the effectiveness of specific immunotherapy (SIT) plus other medical treatments with SIT alone in patients with allergen-triggered asthma.

Searching
MEDLINE was searched from 1966 to 1998 for refereed publications in the English language, using the following keywords: 'asthma', 'allergen', 'immunotherapy', 'hyposensitization', 'study' and 'randomized'. The reference lists in other publications, including identified studies and book chapters, were also examined. Abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled studies (RCTs) with a placebo control were eligible.

Specific interventions included in the review
Treatments in which immunotherapy was administered by injection were eligible. Treatments using other routes of administration, such as oral or sublingual, were excluded. The most commonly administered allergen extract was dust-mite allergen (Dermatophagoides (D.) pteronyssinus). The other allergens included: D. farinae; a combination of D. pteronyssinus and D. farinae; house dust; ragweed pollen; cat dander; grass pollen; Cladosporium herbarum; and assorted allergens. The cointerventions included cromolyn sodium, inhaled corticosteroids, and other unspecified inhaled medication.

Participants included in the review
The inclusion criteria were not defined a priori in terms of the participants, although the focus of the review was stated to be patients with allergen-triggered asthma.

Outcomes assessed in the review
The inclusion criteria were not defined a priori in terms of the outcomes. The outcomes assessed included measures of the following: change in asthma symptoms; pulmonary function; bronchial challenge and cutaneous reactivity; and concomitant medication use, as assessed by the patients' diaries and a standardised scale developed by the investigators. Adverse reactions were also assessed. The outcomes used to assess changes in asthma symptoms in adults were asthma symptoms, daytime asthma symptoms, and daytime breathlessness. The outcomes assessed in children were asthma symptoms, exertion wheeze, and height and weight for age. The outcomes assessed for all ages were: asthma symptoms; symptoms of cat dander exposure; symptoms of dog-dander exposure; exercise tolerant, and nonspecific tolerance of the environment. Pulmonary function was assessed using airways conductance, peak expiratory flow rate (morning, evening and unspecified), forced expiratory volume in 1 second, lung volume, and mid-expiratory flow.

How were decisions on the relevance of primary studies made?
All studies that met the inclusion criteria were included in the meta-analysis.

The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The included studies were restricted to double-blind, placebo controlled RCTs. No formal validity assessment was undertaken.
Data extraction
One author extracted the data. The tables presented in the review suggest that the following data were extracted: the number of participants per treatment group; whether the studies included adults, children or both; allergen administered; and the number of patients with positive and negative outcomes. None of the original data were reanalysed or recomputed. The odds ratios (ORs) and 95% confidence intervals (CIs) of the outcomes were extracted from individual studies.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the population (adults, children, or all ages), then classified according to the conclusion of individual studies regarding the effectiveness of SIT on asthma symptoms (effective, ineffective or equivocal), and the number of studies in each subgroup was counted. The studies were also grouped according to the population studied (adults, children and all ages), and a random-effects model was used to calculate the pooled ORs and 95% CIs for change in asthma symptoms, measures of pulmonary function, results of challenge tests, and use of concomitant medication, using the numbers of patients with positive and negative outcomes. Studies reporting more than one outcome appear to have been included more than once in the same meta-analysis. Comparisons were made of pre- and post-treatment means, and between baseline and treatment means.

How were differences between studies investigated?
The authors do not report whether or how differences between the studies were investigated.

Results of the review
Twenty-four double-blind RCTs (962 patients) were included. Twelve RCTs (301 patients) were restricted to adults, 10 RCTs (592 children) were of children, and 2 studies (64 patients) were not restricted by age.

Information about study sponsorship was not generally available.

Immunotherapy was effective in controlling asthma symptoms. SIT was judged to be effective in 17 of the 24 included studies (71%), ineffective in 4 studies (17%), and equivocal in 3 studies (12%). Chi-squared was 15.25 (d.f.=2, p=0.0005).

Immunotherapy was judged effective regardless of the age of the patients. In adults, 9 of the 12 studies (75%) reported that SIT was effective. In children, 7 of the 10 studies (70%) judged SIT effective. For all ages, one of the 2 RCTs (50%) judged SIT effective.

Immunotherapy significantly improved asthma symptoms. The overall OR (14 outcomes from 9 RCTs) was 2.76 (95% CI: 2.22, 3.42). The improvement was seen in adults (4 outcomes from 3 RCTs, OR 2.77, 95% CI: 1.88, 4.07), and in children (4 outcomes from 4 RCTs, OR 2.21, 95% CI: 1.73, 2.82).

Immunotherapy significantly improved pulmonary function (7 outcomes from 3 RCTs, OR 2.87, 95% CI: 1.82, 4.52, p<0.05).

Immunotherapy gave significant protection against bronchial challenge and cutaneous reactivity. The OR for bronchial reactivity (6 RCTs, 218 patients) was 1.81 (95% CI: 1.32, 2.49), while the OR for cutaneous reactivity (4 RCTs, 121 patients) was 1.83 (95% CI: 1.44, 2.34).

Immunotherapy significantly reduced the use of concomitant medication. The OR (8 outcomes from 5 RCTs) was 2.00 (95% CI: 1.46, 2.72). Adverse reactions (16 RCTs): the methods of defining, quantifying and reporting adverse effects were diverse. The systemic adverse reactions included urticaria, worsening asthma, facial oedema, and rhinoconjunctivitis. These were significantly more common in the immunotherapy-treated group than in the control group; the OR (3 RCTs) was 2.90 (95% CI: 1.54, 5.46). The symptoms resolved rapidly either spontaneously or with medication. Large local reactions were reported in about 25% of the patients (2 RCTs) but were also reported in 48% of the patients in one RCT. Local reactions resolved easily.
Authors' conclusions
The findings suggested that SIT can be effective in the treatment of carefully selected patients with allergen-triggered asthma. In addition, it may be considered for patients with documented allergy whose asthma symptoms are not controlled by standard drug regimens.

CRD commentary
This was a poorly executed systematic review. The aims were stated in the abstract as 'to compare the effects of specific immunotherapy (SIT) plus medical treatment with SIT without medical treatment in patients with asthma'. However, the review appears to compare SIT with a placebo control treatment. The inclusion criteria were defined in terms of the study design and intervention but were not defined a priori in terms of a primary outcome. By restricting the literature search to English language publications identified from one database, other relevant studies may have been omitted. In addition, the lack of attempts to locate unpublished material raises the possibility of publication bias.

The methods used to select the studies were not described. The included studies were restricted to placebo-controlled, double-blind RCTs but no formal validity assessment was undertaken. The data were extracted by one reviewer but relevant information on the individual studies was not presented in the review. Sample size, patient characteristics, baseline medication, the duration of therapy, the timing of outcome assessment, and the number of outcomes assessed in each study were not reported. The studies were combined by classifying them according to the reported conclusions regarding the effectiveness of SIT and then counting the number of studies in each category, but there was no definition of these categories and no exploration of differences between the studies. It appears that more than one outcome from the individual studies was included in the meta-analyses; this was inappropriate and might have led to bias in the estimates of the pooled OR. In addition, statistical heterogeneity was not assessed. The incidence of adverse reactions was reported and discussed. In view of the methodological deficiencies highlighted, the authors' conclusions cannot be considered to be supported by the evidence.

Implications of the review for practice and research
Practice: The authors state that SIT can be effective in the treatment of carefully selected patients with allergen-triggered asthma. In addition, it might be considered for patients with documented allergy whose symptoms are not controlled by standard drug regimens. These recommendations should be viewed with caution in view of the methodological limitations of the review.

Research: The authors did not state any implications for further research.

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