Duration of allergen immunotherapy in respiratory allergy: when is enough, enough?
Cox L, Cohn J R

CRD summary
The authors concluded that clinical relapse rates after the discontinuation of immunotherapy varied and decisions about stopping or continuing immunotherapy must be made on an individual basis. The reliability of the authors' conclusions is unclear given the limitations in the literature search, poor reporting of review methods and the absence of any assessment of individual study quality.

Authors' objectives
To determine the duration of the clinical effects of specific inhalant subcutaneous immunotherapy (SCIT) after discontinuation and identify biomarkers or predictors associated with relapse. This abstract focuses on the duration of clinical efficacy.

Searching
PubMed was searched from 1976 to 2006 using the reported search terms. In addition, articles known to the authors and references in reviews were included.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) with a placebo group and open observational studies were eligible for inclusion.

Specific interventions included in the review
Studies of the discontinuation of SCIT were eligible for inclusion. Studies of venom immunotherapy were also included, but are not considered further in this abstract since they were not the focus of the review. Most of the included studies evaluated immunotherapy to grass (including rye grass); others evaluated dust mite, cat and dog, birch and ragweed allergen immunotherapy.

Participants included in the review
Inclusion criteria were not specified in terms of the participants. The included studies were in adults and children with asthma, allergic rhinitis and rhinoconjunctivitis.

Outcomes assessed in the review
Studies that assessed the clinical efficacy of the primary allergic disease after the discontinuation of immunotherapy were eligible for inclusion. Studies designed to assess the ability of SCIT to prevent the progression of allergic disease, such as the development of asthma or new allergen sensitisation, were excluded from the review unless persistent efficacy was assessed. The studies assessed outcomes between 1 and 12 years after the discontinuation of immunotherapy. The review assessed relapse, symptoms, medication use and the results of various skin and provocation tests.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Percentage values were reported where available.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the immunotherapy allergen and each study was described in the text.

How were differences between studies investigated?
Differences between the studies were apparent from the text and tables.

Results of the review
Eight studies (n=343) were included: one RCT (n=108), four double-blind, placebo-controlled trials (n=131), one non-randomised controlled open study (n=28) and two open observational studies (n=76).

Only clinical outcomes (symptoms and mediation use) are reported below. The review also reported the results of skin testing.

Dust mite: one open study (20 adults and children with asthma treated with 12 to 96 months’ immunotherapy) reported a relapse rate of 55% within 3 years after immunotherapy discontinuation.

Cat and dog: one double-blind, placebo-controlled study (32 patients with dog- or cat-induced asthma treated with 3 years immunotherapy) reported 56% (17 out of 30) of patients with unchanged and 30% (9 out of 30) with improved tolerance in the 5 years since immunotherapy had been discontinued.

Grass pollen: 4 studies were identified. One double-blind, placebo-controlled study (32 patients with severe grass pollen allergic rhinitis treated for 3 to 4 years with SCIT then allocated to continued immunotherapy or placebo) reported no difference between continued immunotherapy and placebo in medication or symptom scores at 3 years. One double-blind, placebo-controlled study (108 patients with seasonal rhinoconjunctivitis treated with 3 years rye/grass pollen immunotherapy) reported an increasing number of patients with worsening symptoms in the 4 years after immunotherapy discontinuation (3% in year 1, 16% in year 2, 30% in year 3 and 33% in a subset of 67 patients at year 4). Most patients (70% of a subgroup of 40 patients) who relapsed responded to pre-seasonal booster immunotherapy. One open controlled study (28 children with allergic rhinoconjunctivitis allocated to 3 years’ grass immunotherapy or pharmacological treatment if SCIT was refused) reported that children (13 of the 14 followed up) in the immunotherapy group had significantly lower total symptom scores and individual symptoms plus combined symptom and medication scores 6 years after discontinuation of immunotherapy compared with the pharmacology treated group (10 of the 14 followed up). A high-percentage required medication for treating seasonal symptoms (69% of immunotherapy group and 80% of control group). Twelve years after immunotherapy was discontinued (12 patients in the immunotherapy group and 10 in the control group), a follow-up study reported significantly lower symptoms in the immunotherapy group and significantly fewer new sensitisations. One double-blind placebo-controlled study (38 adults treated with 2.5 years’ grass pollen immunotherapy) reported low medication and symptom scores 6 years after discontinuation of immunotherapy compared with end-of-treatment results.

Birch pollen: one open study (36 patients with asthma and rhinitis treated with 3 years’ birch pollen immunotherapy) reported that improvement was maintained in 86% of rhinitis and 68% of asthma patients, 6 years after discontinuation of immunotherapy.

Ragweed: one double-blind placebo-controlled study (28 adults with ragweed rhinitis treated with at least 3 years’ immunotherapy, then randomised to continued immunotherapy or placebo for 1 year) reported no significant difference between treatment groups in symptom scores.

Authors’ conclusions
Clinical relapse rates after the discontinuation of immunotherapy varied. Decisions about stopping or continuing immunotherapy must be made on an individual basis.

CRD commentary
The review question was clear with respect to the intervention. Inclusion criteria were broad for the study design and outcomes and not defined for the participants. Only one database, the authors’ files and reference lists were searched; this might have resulted in the omission of other relevant studies and raises the potential for publication bias. It was not
clear whether any language limitations had been applied. Study validity was not assessed, so the results from these studies and any synthesis may not be reliable. In addition, the methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. In view of the differences between the studies, a narrative synthesis with studies grouped by allergen used for immunotherapy was appropriate. However, the individual studies were described rather than the evidence synthesised, and the variety of reported outcome measures made comparisons among studies difficult to interpret. Overall, the reliability of the authors' conclusions is unclear, owing to limitations in the literature search, poor reporting of the review methods and the absence of any specific assessment of individual study quality.

Implications of the review for practice and research
Practice: The authors stated that until adequate information is available, decisions about stopping or continuing immunotherapy must be made on an individual basis.

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

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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.