

Review article

Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis*

Allergic rhinitis is a common condition which, at its most severe, can significantly impair quality of life despite optimal treatment with antihistamines and topical nasal corticosteroids. Allergen injection immunotherapy significantly reduces symptoms and medication requirements in allergic rhinitis but its use is limited by the possibility of severe systemic reactions. There has therefore been considerable interest in alternative routes for delivery of allergen immunotherapy, particularly the sublingual route. The objective was to evaluate the efficacy of sublingual immunotherapy (SLIT), compared with placebo, for reductions in symptoms and medication requirements. The Cochrane Controlled Clinical Trials Register, MEDLINE (1966–2002), EMBASE (1974–2002) and Scisearch were searched, up to September 2002, using the terms (Rhin* OR hay fever) AND (immunotherap* OR desensiti*ation) AND (sublingual). All studies identified by the searches were assessed by the reviewers to identify Randomized Controlled Trials involving participants with symptoms of allergic rhinitis and proven allergen sensitivity, treated with SLIT or corresponding placebo. Data from identified studies was abstracted onto a standard extraction sheet and subsequently entered into RevMan 4.1. Analysis was performed by the method of standardized mean differences (SMD) using a random effects model. $i > P$ -values < 0.05 were considered statistically significant. Subgroup analyses were performed according to the type of allergen administered, the age of participants and the duration of treatment. Twenty-two trials involving 979 patients, were included. There were six trials of SLIT for house dust mite allergy, five for grass pollen, five for parietaria, two for olive and one each for, ragweed, cat, tree and cupressus. Five studies enrolled exclusively children. Seventeen studies administered the allergen by sublingual drops subsequently swallowed, three by drops subsequently spat out and two by sublingual tablets. Eight studies involved treatment for less than 6 months, 10 studies for 6–12 months and four studies for greater than 12 months. All included studies were double-blind placebo-controlled trials of parallel group design. Concealment of treatment allocation was considered adequate in all studies and the use of identical placebo preparations was almost universal. There was significant heterogeneity, most likely due to widely differing scoring systems between studies, for most comparisons. Overall there was a significant reduction in both symptoms (SMD -0.42 , 95% confidence interval -0.69 to -0.15 ; $P = 0.002$) and medication requirements [SMD -0.43 (-0.63 , -0.23); $P = 0.00003$] following immunotherapy. Subgroup analyses failed to identify a disproportionate benefit of treatment according to the allergen administered. There was no significant reduction in symptoms and medication scores in those studies involving only children but total numbers of participants was too small to make this a reliable conclusion. Increasing duration of treatment does not clearly increase efficacy. The total dose of allergen administered may be important but insufficient data was available to analyse this factor.

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Background

Allergic rhinitis is a condition characterized by sneezing, watery nasal discharge, nasal obstruction and itching. It is an increasingly prevalent condition, particularly in the Western world where it affects around 20% of the adult population. Allergic rhinitis is divided into seasonal allergic rhinitis (hay fever) which is triggered by pollens and moulds and perennial allergic rhinitis in which house dust mites and pet dander are the predominant triggers. The spectrum of severity is wide and includes a significant number of sufferers with severe symptoms that are resistant to treatment with usual pharmacotherapy (antihistamines and topical nasal corticosteroids). In such individuals allergen injection immunotherapy is effective in reducing symptoms and medication requirements (1, 2) – effects which persist after withdrawal of treatment (3).

Injection immunotherapy involves the weekly injection of incremental doses of allergen extract until a maintenance dose is reached. Maintenance injections are then given monthly for 2–3 years. The mechanism of action of this form of treatment is not yet fully understood but relevant observations include changes in serum antibody levels (4), reduced sensitivity to allergen injected into the skin or sprayed into the nose (5) and an alteration in the characteristics of T lymphocytes, the key orchestrating cells of the immune response within the nasal mucosa, from an allergic (Th2) profile to a nonallergic (Th1) profile (6) suggesting a modulation of the response of the local immune system to allergen. Immunotherapy is therefore the only current treatment which has the potential to modify the disease process.

Injection immunotherapy is not, however, without problems. Injections can be uncomfortable and minor adverse events such as injection site swelling occur frequently. Systemic reactions are uncommon and anaphylaxis is rare but occasional fatalities have been reported (7). For these reasons a safer route for the delivery of immunotherapy has been sought. Nasal administration is effective but use may be limited by local side effects (nasal discharge, blockage and sneezing) which is also the case for bronchial administration (wheeze and breathlessness). Studies assessing the oral route have indicated a lack of efficacy, presumably due to failure of absorption of the allergen. Attention has therefore focussed on the sublingual route, in which the allergen extract is held under the tongue to allow absorption through the sublingual mucosa.

Standardized allergen extracts can be administered frequently and to a high cumulative dose via the sublingual region and trials so far have shown few adverse effects prompting widespread use in Southern Europe and by some practitioners in Australia. The latest international guidelines (8) conclude that nasal and sublingual immunotherapy (SLIT) may be a viable

alternative to injection immunotherapy but that further studies were needed to determine the most appropriate patients and dosage.

Several trials have been reported recently assessing this form of treatment.

Objectives

To evaluate the efficacy of SLIT compared with placebo or injection immunotherapy for:

- (1) Reductions in symptoms and/or medication requirements during naturally occurring allergic rhinitis.
- (2) Alteration of immunological markers in blood and immunological markers and allergen sensitivity in target organs (nose, eye, skin).

Criteria for considering studies for this review.

Types of studies

All randomized blinded placebo controlled clinical trials.

Types of participants

Persons of any age with a history of allergic rhinitis with or without allergic conjunctivitis, with or without asthma, for whom the allergen is identified and patient sensitivity proven by positive skin prick tests or high circulating levels of allergen-specific IgE antibody detected by radioallergosorbent test (RAST). Trials dealing with asthma alone were excluded. Individuals had to have no other clinically relevant allergen sensitivities.

Types of interventions

Immunotherapy delivered by the sublingual route, whether or not the allergen was subsequently swallowed. All appropriate allergens were considered at all doses and all durations of treatment.

Types of outcome measures

Primary.

- (1) Symptom scores however recorded (e.g. daily or weekly symptom diaries, Visual Analogue Scores, overall assessments).
- (2) Scores referring to concurrent use of anti-allergic medication.

Secondary.

- (3) Assessments of allergen sensitivity in eye, nose or skin.
- (4) Measurements of serum IgE and IgG antibodies.
- (5) Adverse event reports.

Search strategy for identification of studies

Searches (completed in September 2002) were made of the Cochrane Controlled Clinical Trials Register, MEDLINE (1966–2002), EMBASE (1974–2002) and Scisearch by the reviewers using the terms: (Rhin* OR hay fever) AND (immunotherap* OR desensiti*ation) AND (sublingual). *Note:* rhin* covers rhinitis, rhinopathy, rhinosinusitis and rhinoconjunctivitis.

Abstracts of relevant conferences were searched and other trials were identified through discussion with specialist allergist colleagues and professional acquaintances with an interest in the area to enquire whether they were aware of any unpublished or ongoing trials meeting the selection criteria. Reference lists of recent reviews and published trials were searched.

Methods of the review

Quality assessment

Inclusion of studies in the review was decided by discussion between two of the reviewers (DRW, SRD) after all of the studies had been read by DRW. Further information was sought from study authors where needed. The selected studies were then further evaluated for methodological quality to select those suitable for meta-analysis.

Each of the suitable reports were read in detail by DRW and relevant details were abstracted on to a standard extraction sheet (covering study type and methodology; number and description of subjects; details of type, dosage and time schedule/duration of intervention; type, timing and measurement method of outcomes). Concealment of allocation and blinding of study participants and investigators was assessed according to the guidelines of the Cochrane Collaboration.

Due to prior familiarity with the content of most studies author names were not removed before assessment.

Data analysis

Outcome data, extracted from the included studies, was entered into RevMan 4.1 for statistical analysis. All outcome data analysed was continuous (symptom scores, medication scores, antibody levels) but authors used a wide variety of scoring systems and scales for symptoms (most frequently a daily quantification of nasal, eye and chest symptoms entered on a diary card and subsequently totalled and averaged) and medication use (typically a daily score reflecting use of eye drops, nasal sprays and anti-histamine tablets entered on a diary card and subsequently totalled and averaged). Analysis was therefore performed by the method of standardized mean differences (SMD), expressing the difference in means

between immunotherapy and placebo recipients in units of the pooled standard deviation. Random effect models were used to obtain summary statistics for the overall efficacy of SLIT, presented as SMDs with 95% confidence intervals. Chi-square tests were performed to assess heterogeneity between studies, with a *P*-value < 0.1 indicating significant differences between studies.

The following subgroup comparisons were proposed prior to undertaking the data analysis:

- (1) Seasonal vs perennial allergens.
- (2) Children vs adults.
- (3) Dosage of major allergen (< 5 mcg major allergen vs 5–20 mcg vs > 20 mcg: based on WHO guidelines).
- (4) Duration of immunotherapy (< 6 months vs 6–12 months vs > 12 months: in order to cover pre-seasonal, perennial and prolonged treatment).
- (5) Sublingual spit vs sublingual swallow.

Where appropriate, additional analyses were performed according to subgroup.

Description of studies. Searches performed according to the protocol identified 78 abstracts of which 48 were immediately considered unsuitable for inclusion (review articles, descriptive studies, other routes of allergen administration). An additional three studies were identified from personal communication (Fig. 1). A total of 33 full papers were therefore reviewed of which eight were

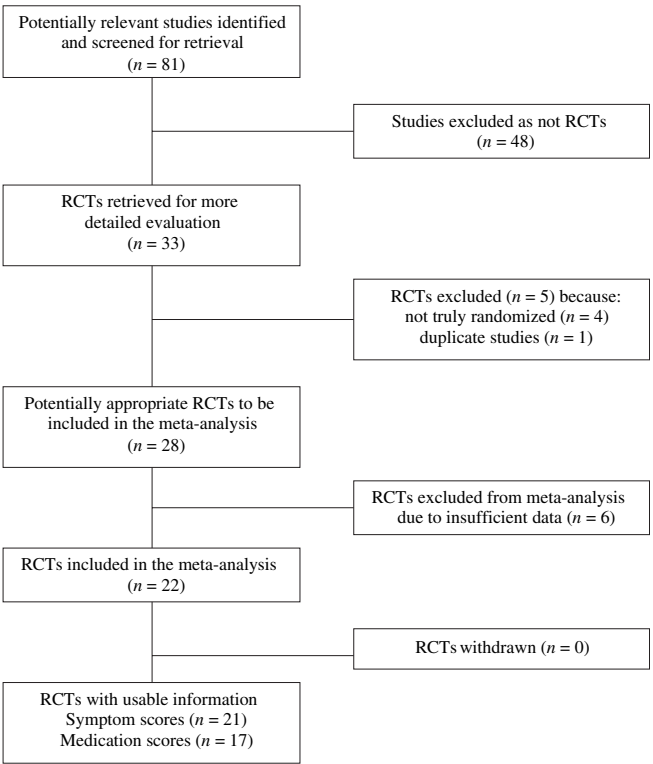


Figure 1. Flowchart showing selection of studies for inclusion in meta-analysis.

Table 1. Characteristics of included studies

First author	Allergen	n (active)	n (placebo)	Adult/child	Duration
Andre (9)	Ragweed	55	55	Adults	7.5 months
Ariano (10)	Cupressus	10	10	Adults	8 months
Bahceciler (11)	HDM	8	7	Children	5 months
Casanovas (12)	Olea	9	6	Adults	2 months
D'Ambrosio (13)	Parietaria	15	15	Adults	8 months
D'Ambrosio (14)	Parietaria	14	16	Adults	9 months
Feliziani (15)	Grass	18	16	Adults	3 months
Guez (16)	HDM	36	36	Mixed	24 months
Hirsch (17)	HDM	15	15	Children	12 months
Hordijk (18)	Grass	35	36	Adults	3 months
La Rosa (19)	Parietaria	20	21	Children	24 months
Lima (20)	Grass	28	28	Adults	12–18 months
Mungan (21)	HDM	15	11	Adults	65 Days
Nelson (22)	Cat	20	21	Adults	105 Days
Passalacqua (23)	HDM	10	10	Adults	24 months
Passalacqua (24)	Parietaria	15	15	Adults	6 months
Pradallier (25)	Grass	63	63	Adults	5 months
Quirino (26)	Grass	10	–	Adults	12 months
Tari (27)	HDM	34	32	Children	18 months
Troise (28)	Parietaria	15	16	Adults	10 months
Voltolini (29)	Tree	15	15	Adults	Preseasonal
Vourdas (30)	Olea	34	32	Children	6 months for 2 yr

excluded [not randomized/controlled (4), insufficient information for analysis (3), duplicate study (1)] and three remain pending – awaiting additional information or data from authors.

Twenty-two studies are therefore included in this analysis. The methods, participants, interventions and outcomes of the included studies are listed in the table of characteristics of included studies (Table 1).

A wide range of allergens were administered in these studies [house dust mite (six), grass (five), parietaria (five), olea (two), ragweed, cat, tree, cupressus (each one)]. Five studies enrolled exclusively children. Seventeen studies administered the allergen by sublingual drops subsequently swallowed, three by drops subsequently spat out and two by sublingual tablets.

The duration of maintenance treatment and the period of follow-up varied considerably between studies, largely reflecting preseasonal, co-seasonal and perennial administration. Using treatment durations identified in the protocol eight studies involved treatment for less than 6 months, 10 studies for 6–12 months and four studies for greater than 12 months.

It was not possible from most of the studies to determine accurately the dose of allergen given in terms of micrograms of major allergen.

Methodological quality of included studies. All included studies were double-blind placebo-controlled trials of parallel group design. Concealment of treatment allocation was considered adequate in all studies – based on statements made by the original authors. Blinding of study subjects and investigators was almost universally main-

tained by use of identical placebo preparations. It should, however, be noted that most investigators reported high levels of minor oral side effects (tingling, itching and swelling beneath the tongue) in actively treated subjects.

Results

Symptom scores

All of the included studies reported symptom scores, recorded in patient diaries, as a primary outcome measure. Data obtained in this way is almost always nonparametric and therefore many studies reported results expressed as median values. Strenuous attempts were made to obtain mean (SD) data direct from authors and studies were only included after this data was obtained. One study (26) compared SLIT with injection immunotherapy rather than with placebo and was therefore excluded from the analysis. From the remaining 21 studies data from 484 immunotherapy recipients and 475 placebo recipients were included. The combined SMD for symptom scores following SLIT was -0.42 [95% confidence interval -0.69 to -0.15 ($P = 0.002$)] indicating a significant reduction in symptoms (Fig. 2). There was, however, significant heterogeneity between studies (chi-square = 75.36; $P < 0.00001$).

Subgroup analyses (Table 2). For studies involving seasonal allergens ($n = 14$, SLIT subjects 346, placebo subjects 344) combined SMD was -0.30 (-0.53 ; -0.07 , $P = 0.01$). Chi-square was 26.91, $P = 0.013$ indicating significant heterogeneity.

For studies involving perennial allergens ($n = 7$, SLIT subjects 138, placebo subjects 131) combined SMD was -0.58 (-1.28 ; 0.12 , $P = 0.11$). Chi-square was 30.66, $P < 0.00001$ indicating significant heterogeneity.

Three individual allergens were used in more than two studies:

house dust mite ($n = 6$, SLIT subjects 118, placebo subjects 110) combined SMD -0.58 (-1.43 ; 0.27 , $P = 0.18$);

grass ($n = 4$, SLIT subjects 144, placebo subjects 143) combined SMD -0.37 (-0.74 ; 0 , $P = 0.05$);

parietaria ($n = 5$, SLIT subjects 79, placebo subjects 83) combined SMD -0.29 (-0.6 ; 0.02 , $P = 0.07$).

For studies involving adults only ($n = 16$, SLIT subjects 373, placebo subjects 368) combined SMD was -0.4 (-0.61 ; -0.18 , $P = 0.0003$). Chi-square was 28.17, $P < 0.02$ indicating significant heterogeneity.

For studies involving children only ($n = 5$, SLIT subjects 111, placebo subjects 107) combined SMD was -0.31 (-1.32 ; 0.7 , $P = 0.5$). Chi-square was 47.16, $P < 0.00001$ indicating significant heterogeneity.

Duration of treatment was divided into three categories.

For treatment duration less than 6 months ($n = 8$ SLIT subjects 183, placebo subjects 175) combined SMD

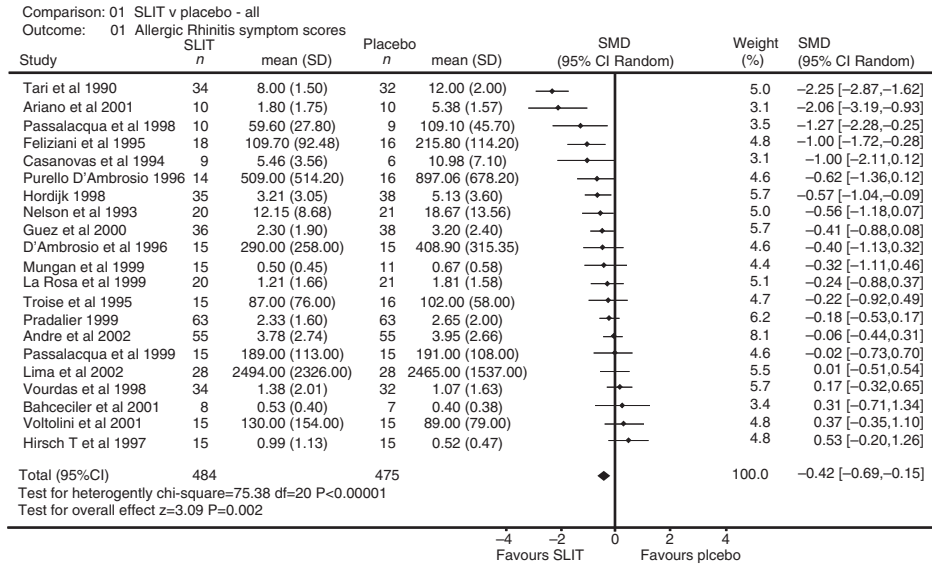


Figure 2. Results of meta-analysis for symptom scores.

Table 2. Subgroup analyses – symptom scores

Subgroup	n (active)	n (placebo)	SMD	95% CI	P-value
Seasonal allergens	346	344	-0.3	-0.53, -0.07	0.01
Perennial allergens	138	131	-0.58	-1.28, 0.12	0.1
Studies involving children only	111	107	-0.31	-1.32, 0.7	0.5
Adult/adult and child studies	373	368	-0.4	-0.61, -0.18	<0.01
Duration <6 months	183	175	-0.36	-0.67, -0.06	0.02
Duration 6–12 months	193	195	-0.21	-0.54, 0.11	0.2
Duration >12 months	108	105	-0.95	-1.97, 0.06	0.07

was -0.36 (-0.67 ; 0.06 , $P = 0.02$). Chi-square was 12.1, $P = 0.1$ indicating lack of heterogeneity.

For treatment duration 6–12 months ($n = 9$, SLIT subjects 193, placebo subjects 195) combined SMD was -0.21 (-0.54 ; 0.11 , $P = 0.2$). Chi-square was 18.46, $P = 0.02$ indicating significant heterogeneity.

For treatment duration over 12 months ($n = 4$, SLIT subjects 108, placebo subjects 105) combined SMD was -0.95 (-1.97 ; 0.06 , $P = 0.07$). Chi-square was 33.31, $P < 0.00001$ indicating significant heterogeneity.

Medication scores

Diary scores reflecting concurrent use of anti-allergic medication were reported in 18 of the 22 studies but the study of Quirino was again excluded. From the 17 remaining studies data from 405 immunotherapy recipients and 398 placebo recipients were included. The combined SMD for medication scores following SLIT was -0.43 (95% confidence interval -0.63 to -0.23) indicating a significant reduction in medication use ($P = 0.00003$) (Fig. 3). Again there was significant heterogeneity between studies but this was less marked (chi-square = 28.48; $P = 0.028$).

Subgroup analyses (Table 3). For studies involving seasonal allergens ($n = 14$, SLIT subjects 346, placebo subjects 344) combined SMD was -0.36 (-0.54 ; -0.18 , $P = 0.00007$). Chi-square was 16.61, $P = 0.22$ indicating lack of heterogeneity.

For studies involving perennial allergens ($n = 3$, SLIT subjects 59, placebo subjects 54) combined SMD was -0.85 (-1.93 ; 0.23 , $P = 0.12$). Chi-square was 10.58, $P = 0.005$ indicating significant heterogeneity.

For individual allergens used in more than two studies: House Dust Mite ($n = 3$, SLIT subjects 59, placebo subjects 54) combined SMD -0.85 (-1.93 ; 0.23 , $P = 0.1$).

Grass ($n = 4$, SLIT subjects 144, placebo subjects 143) combined SMD -0.41 (-0.81 ; -0.01 , $P = 0.04$).

Parietaria ($n = 5$, SLIT subjects 79, placebo subjects 83) combined SMD -0.39 (-0.71 ; -0.08 , $P = 0.01$).

For studies involving adults only ($n = 14$, SLIT subjects 343, placebo subjects 338) combined SMD was -0.51 (-0.73 ; -0.29 , $P < 0.00001$). Chi-square was 22.52, $P = 0.05$ indicating borderline heterogeneity.

For studies involving children only ($n = 3$, SLIT subjects 62, placebo subjects 60) combined SMD was 0.02 (-0.34 ; 0.37 , $P = 0.9$). Chi-square was 0.43, $P = 0.8$ indicating lack of heterogeneity.

For treatment duration less than 6 months ($n = 7$ SLIT subjects 163, placebo subjects 154) combined SMD was -0.63 (-1.09 ; -0.18 , $P = 0.007$). Chi-square was 19, $P = 0.004$ indicating lack of heterogeneity.

For treatment duration 6–12 months ($n = 8$, SLIT subjects 178, placebo subjects 180) combined SMD was -0.35 (-0.6 ; -0.1 , $P = 0.001$). Chi-square was 8.62, $P = 0.28$ indicating lack of heterogeneity.

For treatment duration over 12 months ($n = 2$, SLIT subjects 64, placebo subjects 64) combined SMD was

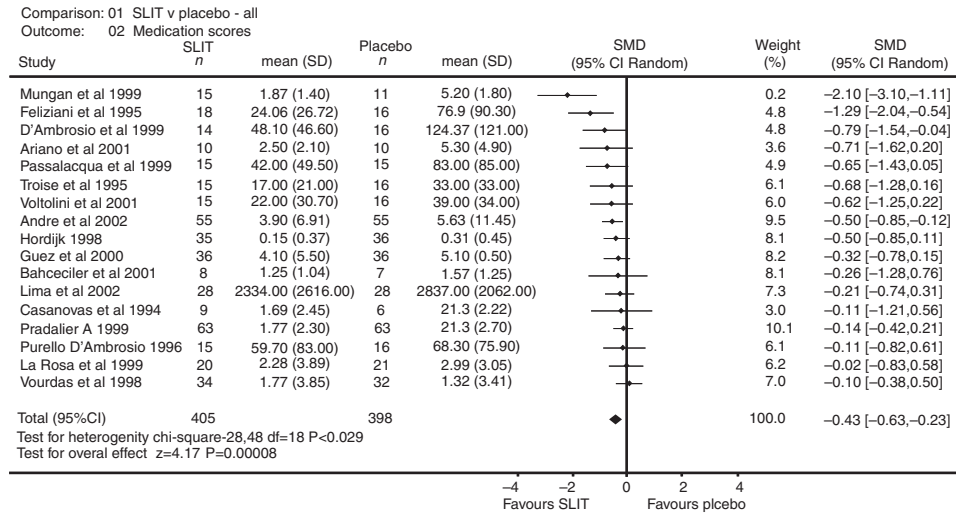


Figure 3. Results of meta-analysis for medication scores.

Table 3. Subgroup analyses – medication scores

Subgroup	n (active)	n (placebo)	SMD	95% CI	P-value
Seasonal allergens	346	344	-0.36	-0.54, -0.18	<0.01
Perennial allergens	59	54	-0.85	-1.93, 0.23	0.12
Studies involving children only	62	60	0.02	-0.34, 0.37	0.9
Adult/adult and child studies	343	338	-0.5	-0.7, -0.29	<0.01
Duration <6 months	163	154	-0.6	-1.09, -0.18	<0.01
Duration 6–12 months	178	180	-0.35	-0.6, -0.11	<0.01
Duration >12 months	64	64	-0.27	-0.62, 0.08	0.13

-0.27 (-0.62; 0.08, $P = 0.13$). Chi-squared was 0.09, $P = 0.76$ indicating lack of heterogeneity.

Serum antibody levels

Serum levels of immunoglobulin (Ig)E and/or IgG were measured before and after treatment in 16 of the 21 included studies. In one study there was no placebo comparison and in a further study total, rather than allergen specific levels were assayed. Detailed data was presented in tabular form in only five studies (one study IgG only) and was available directly from authors for a further one study.

For these studies the combined SMD for changes in allergen-specific IgE ($n = 6$, SLIT subjects 171, placebo subjects 174) was 0.22 (-0.11; 0.55, $P = 0.19$). Chi-square was 10.51, $P = 0.06$.

For allergen-specific IgG4 ($n = 6$, SLIT subjects 190, placebo subjects 191) the combined SMD was 0.6 (-0.11; 1.31, $P = 0.1$). Chi-square was 51.93, $P < 0.00001$.

In the remaining eight studies comments in the published text indicate no significant difference between actively-treated and placebo-treated groups for either IgE or IgG in five studies, no significant difference in IgE but significant increases in IgG4 in two studies and no significant change in IgE (IgG4 not assayed) in one study.

Allergen sensitivity

In 14 of the 21 included studies some measure of allergen sensitivity was performed before and after treatment. Thirteen of these were tests of cutaneous sensitivity, either by skin prick testing, titrated skin prick testing or intradermal testing. In addition studies of nasal sensitivity (4) and conjunctival sensitivity (2) were performed infrequently. The wide variation in methodology and the lack of specific data in the published text made meta-analysis of this data impractical.

For skin sensitivity seven studies reported no significant difference between SLIT and placebo groups, in five there was no data or conclusion drawn and in one there was no placebo comparison.

Adverse events

All of the studies included reported a complete absence of systemic side effects. Minor local side effects consisting of itching and swelling of the oral mucosa were reported almost universally but were rarely of significance.

Discussion

This systematic review of sublingually administered allergen immunotherapy (SLIT) has identified 22 randomized controlled trials with sufficient data for inclusion in meta-analysis. Of the 33 studies initially identified and reviewed in detail, eight were excluded from the analysis, mostly for being open or nonrandomized studies although three studies were excluded because insufficient data was available either from the published manuscript or from direct contact with the authors. Studies were identified from searches of the best available citation databases and from direct communication with key

investigators in the field. Whilst it is never possible to rule out any effects of publication bias due to the nonpublication of studies with negative results it is felt that this is unlikely due to the amount of direct contact the authors have had with the limited number of investigators working in this specialized field.

The methodological quality of the included studies was adequate but this assessment was based on general statements made by the authors of studies in the published text. Most of the papers, particularly those published earlier, do not conform to the CONSORT (1996) guidelines for the publication of randomized controlled trials making the identification of key information regarding randomization methods and concealment of allocation difficult.

Scores representing symptom severity were recorded in all of the included studies and scores quantifying concurrent medication use were recorded in 17 studies. The meta-analysis of these scores confirms that SLIT can significantly reduce both rhinitis symptoms and the requirement for anti-allergic medication. Some caution is required in this interpretation as there was significant heterogeneity between studies although this is felt likely to result predominantly from the wide variety of scoring systems used across studies. Despite this we feel that it is reasonable to meaningfully combine these results and that the consistency, and high degree of statistical significance of the positive treatment effect, allows valid conclusions to be drawn.

Some of the observed variability in treatment effects may be explained by variable responses to treatment according to the type of allergen used, the age of subjects studied or the dose and duration of treatment. As these may be significant factors when selecting suitable individuals for future treatment, additional analyses were performed according to these study characteristics. In almost all cases significant heterogeneity existed between studies and, although this may reflect variability in scoring systems as indicated above, it may be due to incompatibility between smaller numbers of included studies and therefore the results of these analyses should be interpreted with great caution. The subgroup analyses do not strongly indicate a disproportionate benefit for SLIT treatment in any particular patient or disease group but a number of possible trends do emerge.

The seven studies (271 subjects) using perennial allergens (House Dust Mite and Cat) appear to show a similar treatment effect to that observed for seasonal allergens (14 studies; 690 subjects) although the latter was statistically significant, probably as a result of the greater number of subjects. Three allergens (House Dust Mite, grass pollen and parietaria) were used in more than two studies and were therefore subjected to separate meta-analysis. The six House Dust Mite studies formed the bulk of the perennial allergen subgroup and results were similar – falling short of statistical significance for both symptom and medication scores. Both grass pollen and

parietaria, however, did show statistically significant effects although numbers of subjects were small. It may, therefore, be the case that SLIT has greater potential in grass and parietaria sensitive subjects but this is by no means proven by this analysis.

SLIT is a particularly attractive treatment option for children where safety is paramount and outpatient, home-based therapy is clearly preferable. In contrast to the overall effect in adults and children, the treatment effect in children was not significant. These data must be interpreted with great caution as the number of studies assessing only children was small (five studies; 218 subjects) but this analysis suggests that SLIT is not of particular benefit for allergic rhinitis in children. Removing children-only studies from the overall analysis did not change the outcome suggesting consistent beneficial effects in adults.

Increasing duration of treatment beyond 12 months does appear to increase the treatment effect but the number of studies of this duration was small (4) and the result just failed to reach significance. It is theoretically likely that the total dose of allergen administered is relevant to the efficacy of treatment but unfortunately it was not possible to analyse the data divided according to allergen dosage due to the wide range of allergen preparations used and a paucity of information regarding the dose expressed in micrograms of major allergen.

Selected secondary outcome measures were much more difficult to analyse. Not all studies (only 16 of 21) reported measurement of serum antibodies and the wide variety of methods used to assess skin or target organ sensitivity made combining results unfeasible. For those studies reporting changes in serum antibodies only a small number (6) published data suitable for meta-analysis and therefore much of the interpretation is descriptive but does suggest consistent increases in allergen-specific IgG4 in SLIT recipients.

Importantly none of the studies reported significant side effects during SLIT.

Allergen injection immunotherapy is an extremely effective treatment for seasonal allergic rhinitis that has failed to respond to pharmacological measures, resulting in a 50% reduction in symptom scores and an 80% reduction in medication scores. These effects persist for at least 3 years after discontinuation of treatment. These benefits do, however, have to be set against the incidence of severe systemic reactions, including occasional fatalities, during injection immunotherapy. This morbidity has resulted in tight regulation of this form of treatment including recommendations that it be restricted to specialist centres and that patients be observed for up to 1 h after injections making it time-consuming and expensive.

For these reasons a number of alternative routes for therapeutic allergen presentation have been considered and sublingual administration has emerged as the most

likely to be both acceptable and effective. The potential for home administration and the fact that no systemic reaction has yet been reported make this form of treatment extremely attractive. This review and meta-analysis will lend support to the promotion of this treatment but assessment of the magnitude of the effect is difficult making direct comparison with injection immunotherapy impossible. Two of the included studies compared injection immunotherapy with SLIT directly (one with a further placebo arm) (21, 26). These two studies reported similar improvements in symptoms and medication requirements for the two routes of administration.

Injection immunotherapy is felt most likely to exert its effects through modulation of the response of the immune system upon allergen exposure. Giving high doses of

allergen systemically results in changes in both the humoral and cellular components of the immune response felt likely to represent a change from a Th2 predominant response dominated by the cytokines IL-4, IL-5 and IL-13, with the eosinophil as the key effector cell and IgE as the responding antibody, to a Th1 response characterized by an absence of eosinophilia and an IgG antibody response. The role of increases in IgG4 antibodies is unclear and indeed they may play no active role, merely acting as a marker of high dose allergen exposure. Where reported in this review IgG4 levels increase following SLIT, much as they do following injection immunotherapy indicating that a similar immunological change may be initiated. Further mechanistic studies are clearly required.

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