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Allergen injection immunotherapy for seasonal allergic rhinitis (Review)

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[Intervention Review]

Allergen injection immunotherapy for seasonal allergic rhinitis

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ABSTRACT

Background

Allergic rhinitis is the most common of the allergic diseases. Despite improved understanding of the pathophysiology of allergic rhinitis and advances in its pharmacological treatment, its prevalence has increased worldwide. For patients whose symptoms remain uncontrolled despite medical treatment, allergen injection immunotherapy is advised. An allergen-based treatment may reduce symptoms, the need for medication and modify the natural course of this disease.

Objectives

To evaluate the efficacy and safety of subcutaneous specific allergen immunotherapy, compared with placebo, for reducing symptoms and medication requirements in seasonal allergic rhinitis patients.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1 2006), MEDLINE (1950 to 2006), EMBASE (1974 to 2006), Pre-MEDLINE, KOREAMED, INDMED, LILACS, PAKMEDINET, Scisearch, *m*RCT and the National Research Register. The date of the last search was February 2006.

Selection criteria

All studies identified by the searches were assessed to identify randomised controlled trials involving participants with symptoms of seasonal allergic rhinitis and proven allergen sensitivity, treated with subcutaneous allergen specific immunotherapy or corresponding placebo.

Data collection and analysis

Two independent authors identified all studies reporting double-blind, placebo controlled randomised trials of specific immunotherapy in patients with seasonal allergic rhinitis due to tree, grass or weed pollens. Two authors independently performed quality assessment of studies. Data from identified studies were abstracted onto a standard extraction sheet and subsequently entered into RevMan 4.2.8. Analysis was performed using the Standardised Mean Difference (SMD) method and a random-effects model; P values < 0.05 were considered statistically significant. The primary outcome measures were symptom scores, medication use, quality of life and adverse events.

Main results

We retrieved 1111 publications of which 51 satisfied our inclusion criteria. In total there were 2871 participants (1645 active, 1226 placebo), each receiving on average 18 injections. Duration of immunotherapy varied from three days to three years. Symptom score data from 15 trials were suitable for meta-analysis and showed an overall reduction in the immunotherapy group (SMD -0.73 (95% CI -0.97 to -0.50, P < 0.00001)). Medication score data from 13 trials showed an overall reduction in the immunotherapy group (SMD of -0.57 (95% CI -0.82 to -0.33, p<0.00001)). Clinical interpretation of the effect size is difficult. Adrenaline was given in 0.13% (19 of 14085 injections) of those on active treatment and in 0.01% (1 of 8278 injections) of the placebo group for treatment of adverse events. There were no fatalities.

Authors' conclusions

This review has shown that specific allergen injection immunotherapy in suitably selected patients with seasonal allergic rhinitis results in a significant reduction in symptom scores and medication use. Injection immunotherapy has a known and relatively low risk of severe adverse events. We found no long-term consequences from adverse events.

PLAIN LANGUAGE SUMMARY

Immunotherapy by allergen injections for seasonal allergic rhinitis ('hay fever')

Seasonal allergic rhinitis ('hay fever') is a global health problem and its prevalence has increased considerably in the last two decades. Treatment includes allergen avoidance, drugs such as antihistamine tablets and nasal sprays, and immunotherapy (vaccination). For those patients whose symptoms remain uncontrolled despite drug treatment, specific allergen immunotherapy (SIT) is advised.

Specific allergen immunotherapy is most commonly administered as subcutaneous (under the skin) injections by specialists requiring a building-up period followed by a maintenance period of three to five years. Immunotherapy may also be delivered by the oral, nasal or sublingual route and these will be studied in separate Cochrane reviews, as will immunotherapy for perennial (all year round) allergic rhinitis. In this review we aimed to evaluate the efficacy and safety of injection immunotherapy, compared with placebo, for reducing symptoms and the need for medication.

We identified randomised, double-blind, placebo controlled trials of specific allergen immunotherapy in patients with seasonal allergic rhinitis due to tree, grass or weed pollens. Fifty-one studies satisfied our inclusion criteria. In total there were 2871 participants (1645 in the treatment groups and 1226 in the placebo), each receiving on average 18 injections. The duration of treatment varied from three days to three years.

This review has shown that injection immunotherapy in suitably selected patients with hay fever results in significant reductions in symptom scores and medication use. Injection immunotherapy has a known and relatively low risk of severe adverse events. We found no long-term consequences from adverse events and no fatalities.

BACKGROUND

Allergic rhinitis is a significant public health concern in many countries and particularly so in the economically-developed world affecting up to 30% of adults (Gupta 2004; Bauchau 2004) and up to 40% of children (ISAAC 1998). The prevalence of allergic rhinitis has increased considerably in the last two decades, particularly in countries with a Western lifestyle (Fleming 1987; Ninan 1992; Mygind 1996; Jarvis 1998; Wilson 2003; Skoner 2001).

Allergic rhinitis has traditionally been categorised as being either 'seasonal', in which case pollen or moulds are the usual trigger, or 'perennial', in which case house dust mites or pet dander allergens are typically responsible, although in the tropics perennial symptoms can be caused by pollen and mould. However, allergic rhinitis is becoming increasingly assessed according to the frequency of symptoms (i.e. intermittent or persistent) and their severity and impact on patients' quality of life (i.e. mild or moderate/severe) (Bousquet 2001).

Allergic rhinitis is "a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose" (Bousquet 2001). The allergen provokes production of IgE antibodies which bind to mast cells releasing histamine and other inflammatory mediators. This pathway is responsible for immediate symptoms which can begin within a few minutes of exposure to the allergen. IgE production is triggered by T-lymphocytes which also control production of eosinophils and other inflammatory mediators responsible for the delayed reactions occurring a few hours after exposure (Lund 1994). Whilst the mechanism of immunotherapy is not completely understood, the most plausible explanation is that immunotherapy modifies the immune response by producing less of the 'harmful' antibodies (specific immunoglobulin (Ig) E) and more of the 'protective' antibodies called IgG (Frew 1993). Immunotherapy acts on specific cells called T cells, to modify their peripheral and mucosal responses to allergen (Till 2004). This mechanism involves the switching from Th2 response (allergic response) in favour of Th1 response (non-allergic response) (Till 2004).

Clinical symptoms of allergic rhinitis include nasal itching, sneezing, watery nasal discharge, blocked nose and eye symptoms (Durham 1998). Treatment options include allergen avoidance, pharmacotherapy and immunotherapy. Recommended drug treatments include antihistamines, topical nasal steroids, anti-leukotriene receptor antagonists, mast cell stabilisers and, in some cases, a short course of systemic steroids or decongestants. For patients whose symptoms remain uncontrolled despite these treatments, allergen injection immunotherapy is advised (Lund 1994; Malling 2001).

Allergen immunotherapy by injection (also known as desensitisation or hyposensitisation) consists of an induction course of injections of increasing doses of the allergen extract, usually given weekly or fortnightly. The maintenance phase of maximum dosage injections usually lasts between two to three years (Frew 1993). Immunotherapy can also be delivered through the nasal, oral or sublingual (under the tongue) route; its efficacy by the sublingual method of delivery is the subject of a separate recently completed review (Wilson 2003; Wilson 2005). The effectiveness of immunotherapy by the oral and nasal route will also be studied in separate Cochrane reviews. Although injections can consist of mixed allergen extracts, there is some evidence that this can lead to degradation of the allergenic compounds, reducing the effect of the treatment (Dreborg 1992).

Specific allergen immunotherapy (SIT) for hay fever is widely considered to be effective where grass pollen (Varney 1991; Malling 2001), ragweed, and birch pollen (Viander 1978) are causal agents, and there is evidence that its efficacy may continue for many years beyond the treatment period (Mosbech 1988; Durham 1999b). However, there are concerns over its safety. In 1986 a report by the UK Committee on the Safety of Medicines (CSM 1986) suggested that deaths and adverse reactions from allergen immunotherapy were increasing. The UK Committee on the Safety of Medicines stipulated that this treatment be given only where full resuscitation facilities were available and that patients be observed for at least two hours after its administration. Although observation time was later reduced to one hour (CSM 1994), these restrictions effectively prevented administration of allergen immunotherapy in primary care in the UK, with the effect that availability was severely curtailed.

Not all sufferers are suitable candidates for this therapy. Some 13% to 38% of people with seasonal allergic rhinitis also suffer from asthma (Aberg 1989) and asthma sufferers have been identified as a group with a particularly high risk of adverse reactions and death from immunotherapy. For these reasons, many countries do not recommend immunotherapy in people with asthma, which excludes a large proportion of the population which might otherwise benefit. Despite the reduced availability of immunotherapy in the UK and Scandinavian countries, immunotherapy is still freely practiced in parts of Europe and in North America (Norman 1990; CSACI 1995).

There are many issues in immunotherapy which merit further investigation such as the possible long-term benefits of immunotherapy for seasonal allergic rhinitis or the suitability of this treatment for patients who also suffer from asthma. In this review, however, we focus on two key and fundamental questions: we intend to examine the efficacy and efficacy-risk profile of pollen immunotherapy for seasonal allergic rhinitis.

OBJECTIVES

To evaluate the efficacy and safety of subcutaneous allergen specific immunotherapy compared with placebo in seasonal allergic rhinitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind, placebo controlled trials.

Types of participants

Patients with seasonal allergic rhinitis due to tree, grass or weed pollens. We stipulated that allergy must be proven using an objective test such as positive skin prick tests or high circulating levels of allergen-specific IgE antibody detected by a specific blood test for allergy called radioallergoabsorbent test (RAST). Trials dealing with perennial allergic rhinitis and asthma alone were excluded.

Types of interventions

Multiple injections of high dose immunotherapy with standardised single allergen extracts compared with placebo. All appropriate allergens were considered at all doses and all durations of treatment.

Types of outcome measures

Primary outcome measures

Symptomatic

Symptom scores: typically collected using symptom diaries (any permitted);
Patient-completed visual analogue rhinitis symptoms scores.

Clinical

Medication use;
Rhinoconjunctivitis quality of life questionnaire;
Compliance, i.e. whether patient completed treatment;
Doctor-completed visual analogue rhinitis symptom scores;
Adverse reactions: local (for example, swelling, itchiness) and systemic (for example, anaphylaxis);
Time to onset (in minutes) of systemic reactions.

Secondary outcome measures

Experimental outcomes as recorded in trials, such as skin reactivity (immediate phase (15 minutes) and late phase (6 to 24 hours)) and levels of specific IgE and IgG antibodies. These were deemed to be of secondary importance because their clinical usefulness is yet to be adequately established.

Search methods for identification of studies

Published, unpublished and ongoing studies were identified from the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 1 2006), MEDLINE (1950 to 2006), EMBASE (1974 to 2006), KOREAMED, INDMED, LILACS, PAKMEDINET, Scisearch, *m*RCT and the National Research Register. The date of the last search was February 2006.

The following search strategy was used to search CENTRAL:

#1 RHINITIS ALLERGIC SEASONAL single term (MeSH)
#2 hayfever OR hay NEXT fever OR pollinosis OR pollenosis OR SAR OR pollen NEAR allerg*
#3 #1 OR #2
#4 RHINITIS single term(MeSH)
#5 rhiniti*
#6 #4 OR #5
#7 season* OR spring OR summer OR pollen OR grass* OR birch OR ragweed OR tree* OR weed* OR mugwort OR willow OR alder
#8 #6 AND #7
#9 #3 OR #8
#10 DESENSITIZATION IMMUNOLOGIC single term (MeSH)
#11 ALLERGENS [im] single term (MeSH)
#12 ALLERGENS [tu] single term (MeSH)
#13 ALLERGENS [ad] single term (MeSH)
#14 IMMUNOTHERAPY single term (MeSH)
#15 POLLEN [im] single term (MeSH)
#16 POACEAE [im] single term (MeSH)
#17 DOSE RESPONSE RELATIONSHIP, IMMUNOLOGIC single term (MeSH)
#18 immunotherapy OR immunomodulatory OR immune NEAR therapy OR immunologic NEAR response* OR allergen* OR antigen* OR desensiti* OR hyposensiti*
#19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 #9 AND #19

All other search strategies were modelled on the CENTRAL version. The terms were combined with the highly sensitive search strategy for identifying clinical trials, described in Appendix 5c of the Cochrane Reviewers' Handbook, to search MEDLINE.

We considered studies published in languages other than English if the translated abstract indicated that the study was a randomised controlled trial of subcutaneous allergen specific immunotherapy for seasonal allergic rhinitis and we used translators provided by the Cochrane ENT Group.

The bibliography of each paper and of other published reviews was checked for further references. The primary author of each study was contacted to identify additional published and unpublished studies.

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.

Data collection and analysis

Study selection

Three independent authors (MC, BA, MJ) checked titles and abstracts identified from the searches. Both authors obtained the full text of all studies of possible relevance for assessment. The authors (MC, BA, MJ) read all abstracts and decided which trials met the inclusion criteria and graded their methodological quality. Any disagreement was resolved by discussion between the authors with recourse to a third reviewer (AS or SD) for arbitration where necessary. Authors were contacted for clarification where necessary. Further information was sought from study authors when needed. The selected studies were then further evaluated for methodological quality to select those suitable for meta-analysis.

Data extraction

Each of the suitable reports were read in detail by MC, BA and MJ 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.

Quality assessment

Methodological quality was assessed using the following approach:

Concealment of allocation to the intervention or placebo arm of trial

A - Adequate; for example, centralised randomisation by a central office.
B - Unclear; list or table or apparently adequate concealment but no other information in trial.
C - Unmet; alternation, days of the week, any allocation that is potentially transparent.

Attrition bias

A - Adequate; trials where an intention to treat analysis is possible and drop out rate was less than 20% after one year in all groups.
B - Unclear; trials where drop out rate was more than 20% after one year or large differences in drop out rates between groups were observed.
C - Unmet; No reporting on drop out rates and intention to treat analysis not possible.

Detection bias

A - Adequate; trials in which blinding of investigators assessing outcomes was adequate.
B - Unclear; trials in which blinding of investigators was not described adequately.
C - Unmet; trials in which blinding of investigators was clearly not performed.

Trials which fell into allocation concealment category C were excluded from the analysis and the remaining studies were given an overall score using the following criteria:
A - Low risk of bias, where all criteria were 'Adequate'.
B - Medium risk of bias, where one or more criteria were 'Unclear' and the rest were 'Adequate'.
C - High risk of bias, where one or more criteria were unmet.

Study quality was used in a sensitivity analysis. Due to prior familiarity with the content of most studies, authors names were not removed before assessment.

Data analysis

Outcome data, extracted from the included studies, were entered into RevMan 4.2.8 for statistical analysis. All outcome data on efficacy that were analysed were continuous (symptom scores, medication scores) but authors used a wide variety of scoring systems and scales for symptoms (most frequently a daily quantification of nasal, ocular and chest symptoms entered on a diary card and subsequently totalled and averaged) and rescue medication use (typically a daily score reflecting use of oral antihistamines tablets, eye drops and nasal sprays entered on a diary card and subsequently totalled and averaged).

Adverse reactions (dichotomous outcome) were recorded by people or by injection, as local or systemic reactions. Systemic reactions were graded according to time of onset (early within 30 minutes and late after 30 minutes) and severity of reaction. For assessing the severity of systemic reactions we followed the grading system proposed in the Position Paper of the European Academy of Allergology and Clinical Immunology on Immunotherapy (Malling 1993):

Grade 1: Non-specific reactions: Reactions probably not IgE-mediated; i.e. discomfort, headache, arthralgia, etc.
Grade 2: Mild systemic reactions: Mild rhinitis and/or asthma (peak expiratory flow rates (PEFR) over 60% of predicted or of the personal best values) responding adequately to antihistamines or inhaled B2-agonists.
Grade 3: Non life-threatening systemic reactions: Urticaria, angioedema, or severe asthma (PEFR under 60% of predicted or of personal best values) responding well to treatment.
Grade 4: Anaphylactic shock: Rapidly evoked reaction of itching, flushing, erythema, bronchial obstruction, etc. requiring intensive treatment.

Two key analyses were carried out:
An examination of the efficacy of immunotherapy during the period of the treatment;
An examination of the risks of serious adverse reactions due to treatment.

Quantitative analyses of outcomes were presented on an intention-to-treat basis. Meta-analysis was performed, where appropriate, using a random-effects model to obtain summary statistics for the overall efficacy of subcutaneous immunotherapy. We planned to express categorical data as odds ratios or relative risks (with 95% confidence intervals). For continuous data, the Standardised Mean Difference (SMD) was calculated (with 95% Confidence Intervals). SMD standardises the outcome for each individual study to the effect size found in terms of the standard deviation observed (in the study). The use of SMD is generally the method used for pooling data from different scales. Chi-squared tests were performed to assess heterogeneity between studies, with a P value <0.05 indicating significant differences between studies.

The following subgroups of comparisons between active and placebo treated subjects were proposed prior to undertaking the data analysis:

1 - SYMPTOM SCORES
2 - MEDICATION SCORES
3 - SYMPTOM AND MEDICATION SCORES
4 - NASAL SYMPTOM SCORES
5 - BRONCHIAL SYMPTOM SCORES
6 - OCULAR SYMPTOM SCORES
7 - GLOBAL IMPROVEMENT
8 - RHINOCONJUNCTIVITIS QUALITY OF LIFE
9 - ADVERSE EVENTS
9.1 - LOCAL REACTION
9.1.1 - Local reaction not requiring treatment
9.1.2 - Local reaction requiring treatment
9..2 - SYSTEMIC REACTION
9.2.1 - Early systemic reaction grade 2 (< 30 minutes)
9.2.2 - Early systemic reaction grade 3 (< 30 minutes)
9.2.3 - Early systemic reaction grade 4 (< 30 minutes)
9.2.4 - Late systemic reaction (> 30 minutes)
9.2.5 - Systemic reaction - severity and time of onset not specified
10 - ADRENALINE USE
11 - COST
12 - SERUM ANTIBODY LEVELS
12.1 - Specific IgG
12.2 - Specific IgG-4
12.3 - Specific IgE
13 - SPECIFIC ALLERGEN CHALLENGES
13.1 - Nasal Challenge
13.2 - Conjunctival Challenge
13.3 - Skin Challenge

13.4 - Bronchial Challenge
14 - DEATHS

Where appropriate, additional analyses were performed according to subgroup.

Characteristics of the treatments and participants with highest and lowest relative risk of adverse reaction were described.

Tests for heterogeneity were performed and if found to be significant, possible explanations were sought through examination of study quality and type of immunotherapy.

We used a funnel plot to investigate the possibility of publication bias.

RESULTS

Description of studies

Our searches identified 1111 abstracts of potential relevance, of which 276 were selected for in-depth appraisal of full text papers. Fifty-one full papers satisfied our inclusion criteria. The methods, participants, interventions and outcomes of the included studies are listed in the table of Characteristics of Included Studies. In total there were 2871 participants: 1645 active and 1226 placebo, each receiving on average 18 injections. All studies included patients with seasonal allergic rhinitis. Symptom score data from 15 trials were suitable for meta-analysis.

Six studies specified that patients did not experience co-existent asthma; in 27 studies patients had mild to moderate seasonal allergic asthma; 18 studies did not specify the asthmatic status of their participants.

A wide range of allergens were administered in these studies: ragweed (12), mixed grass (16), timothy (5), parietaria (6), birch (4), orchard (2), cedar (3), bermuda (1), juniperus ashei (1) and cocos (1).

The types of vaccines used were extracts (38), allergoids (12) and non-specified (1).

The duration of maintenance treatment and the period of follow up varied considerably between studies, largely reflecting pre-seasonal, co-seasonal and post-seasonal administration. Duration of immunotherapy varied from three days (minimum duration) to three years (maximum duration). Six studies did not mention the duration of treatment.

It was not possible from most of the studies to determine accurately the dose of allergen given in terms of micrograms of major allergen. Doses given were quantified in many different units including BU, PNU, BU, SQ-U, mcg Ag, SE-U, Aueq, SU/ml, TU, wt/vol and HEP.

The reasons for excluding the 230 studies were:

Not a double-blind randomised placebo controlled study (23);
Not a double-blind placebo controlled study (16);
Not a double-blind study (7);
Not a placebo controlled study (58);
Not a randomised study (6);
Route other than subcutaneous (12);
Single or low dose immunotherapy (5);
Not a specific immunotherapy study (25);
No standardised allergen extracts used (4);
Rinkel method (very low-dose co-seasonal immunotherapy) (2);
No allergen extract used (4);
Other outcomes investigated (28);
Comparison of two different immunotherapy preparations (3);
Not a seasonal allergic rhinitis study (11);
Patients were asthmatics, not rhinitics (6);
Peptide immunotherapy used (1);
Review article (4);
Follow-up study (1);
Some patients had previous immunotherapy (4);
Survey study (1);
Withdrawal of treatment study (3);
Data included in another paper (5);
Insufficient data for analysis (1).

Risk of bias in included studies

All included studies were double-blind placebo controlled trials of parallel group design. Concealment of treatment, based on statements made by the original authors, was considered adequate in all studies. Blinding of study subjects and investigators was almost universally maintained by use of similar placebo preparations. Overall score for methodological quality was found to be 'low risk of bias' in 42 studies, 'medium risk of bias' in five studies, 'high risk of bias' in one study, and undetermined in three studies. Full details, including quality scores, are set out in the table of 'Characteristics of Included Studies'.

Effects of interventions

The decision to pool studies in the following meta-analyses, despite evidence of heterogeneity, was taken as it was clear for all outcomes that all of the pooled studies showed a consistent direction of effect. We believe the pooled results give an idea of the direction and size of the effect of subcutaneous immunotherapy.

1. Symptom scores

Most of the included studies reported symptom scores, recorded in patient diaries, as a primary outcome measure. Data obtained in this way are almost always non-normally distributed (skewed) and therefore many studies reported results as median values. Strenuous attempts were made to obtain means and standard deviations direct from authors and values were only included after data were obtained. Only 15 studies met all criteria for symptom score meta-analysis; these included active immunotherapy subjects n = 597 and placebo subjects n = 466 (Balda 1998; Bodtger 2002; Bousquet 1990; Brewczynski 1999; Corrigan 2005; Drachenberg 2001; Ferrer 2005; Frew 2006; Jutel 2005; Meriney 1986; Ortolani 1984; Ortolani 1994; Varney 1991; Walker 2001 (Delta values were used for this study); Zenner 1997).

The combined Standardised Mean Difference (SMD) for symptom scores following subcutaneous immunotherapy was -0.73 (95% CI -0.97 to -0.50, P < 0.00001), indicating a significant reduction in symptom scores. There was evidence of significant heterogeneity between studies (P < 0.0005), but no unifying reasons were found to explain the difference of effect in the studies included. See Analysis 1.1.

Frew 2006 is the largest trial assessing the efficacy and safety of SIT for grass pollen allergy conducted to date. The trial was a three arm study: the first active group (n = 203) received standardised depot preparations of grass pollen extract (Alutard SQ-U, Phleum

pratense) at the dosage 100,000 SQ-U, the second active group (n = 104) received the same at the dosage 10,000 SQ-U, and the third group (n = 103) a placebo. Sensitivity analysis was performed by replacing the 100,000 SQ-U data included in the above meta-analysis with the data from the 10,000 SQ-U arm, to test the effect on the result. The revised combined SMD was -0.73 (95% CI -0.97 to -0.49) (P < 0.00001). Significant heterogeneity between studies was still evident (P < 0.0004).

Of the 16 further studies that it was not possible to include in the above meta-analysis all 16 favoured the intervention group. A description of data from these studies can be found in Table 1.

2. Medication scores

Diary scores reflecting concurrent use of anti-allergic medication were reported in 13 studies; these included active immunotherapy participants n = 549 and placebo participants n = 414 (Balda 1998; Bodtger 2002; Bousquet 1990; Brewczynski 1999; Corrigan 2005; Dolz 1996; Drachenberg 2001; Ferrer 2005; Frew 2006; Jutel 2005; Mirone 2004; Varney 1991; Walker 2001 (Delta values were used for this study)). In the study Dolz 1996 the decrease in medical treatment was statistically significant in the springs of 1991 and 1992 (P < 0.01), but not in spring 1990.

The combined SMD for medication scores following immunotherapy was -0.57 (95% CI -0.82 to -0.33, P < 0.00001) indicating a significant reduction in medication scores. There was evidence of significant heterogeneity between studies (P < 0.0009), but no unifying reasons were found to explain the difference of effect in the studies included. See Analysis 1.2.

Sensitivity analysis was again performed for the Frew 2006 study by replacing the 100,000 SQ-U data included in the above meta-analysis with the data from the 10,000 SQ-U arm, to test the effect on the result. The revised combined SMD was -0.56 (95% CI -0.82 to -0.30, P < 0.0001). Significant heterogeneity between studies was still evident (P < 0.0004).

Of the 12 studies that were not included in the meta-analysis, 11 favoured the intervention group. A description of data from these studies can be found in Table 2.

3. Symptom and medication scores

Eight studies were included for symptom and medication score analysis, which comprised active immunotherapy subjects n = 320 and placebo subjects n = 297 (Balda 1998; Corrigan 2005; Drachenberg 2001; Ferrer 2005; Jutel 2005; Ortolani 1994; Pastorello 1992; Zenner 1997).

The combined SMD for medication and symptom scores following subcutaneous immunotherapy was -0.48 (95% CI -0.67 to -0.29, P < 0.00001) indicating a significant reduction in symptom and medication scores in the immunotherapy treated group. There was no evidence of heterogeneity between studies (P = 0.25). See Analysis 1.3.

Of the 16 studies that were not included in the meta-analysis all 16 studies favoured the intervention group. A description of data from these studies can be found in Table 3.

4. Nasal symptom scores

Nine studies were included for nasal symptom score analysis, which comprised active immunotherapy subjects n = 396 and placebo subjects n = 276 (Balda 1998; Bousquet 1987b; D'Amato 1995; Dolz 1996; Ferrer 2005; Frew 2006; Mirone 2004; Zenner 1997). In D'Amato 1995 mean (SD) values for nasal block obtained from visual analogue scores for patients completing two years of treatment (active or placebo) were chosen as representative parameters for meta-analysis. In Dolz 1996 the nasal symptoms improved significantly during the springs of 1991 and 1992, but this result did not occur during spring 1990. In Zenner 1997 median nasal symptom scores and overall symptom scores were significantly lower in the specific immunotherapy group compared to the placebo group (P = 0.014 for nasal symptoms and P = 0.02 for overall symptoms).

The combined SMD for nasal symptom scores following subcutaneous immunotherapy was -1.59 (95% CI -2.29 to -0.89, P < 0.00001) indicating a significant reduction in nasal symptom scores in the immunotherapy treated group. There was evidence of heterogeneity between studies (P < 0.00001), but no reason was found to explain the difference of effect in the studies included. See Analysis 1.4.

Sensitivity analysis was performed for the Frew 2006 study by replacing the 100,000 SQ-U data included in the above meta-analysis with the data from the 10,000 SQ-U arm, to test the effect on the result. The revised combined SMD was -1.59 (95% CI -2.33 to -0.86, P < 0.0001). Significant heterogeneity between studies was still evident (P < 0.00001).

Of the eight studies not included in the meta-analysis, seven favoured the intervention group. A description of data from these studies can be found in Table 4.

5. Bronchial symptom scores

Five studies were included for bronchial symptom score analysis, comprising active immunotherapy subjects n = 266 and placebo subjects n = 163 (Balda 1998; Dolz 1996; Ferrer 2005; Frew 2006; Mirone 2004). In Dolz 1996 the bronchial symptoms showed a statistically significant improvement (P < 0.001) during the springs of 1990 and 1991. In spring 1992, the bronchial symptoms in the active group did not appear. In the placebo group, they were mild in the first days. All patients took bronchodilator and/or inhaled corticoids every day during the spring and summer. Therefore, the bronchial symptom scores in this group were not easily registered.

The combined SMD for bronchial symptom scores following subcutaneous immunotherapy was -0.59 (95% CI -1.06 to -0.11, P = 0.02) indicating a significant reduction in bronchial symptom scores in the immunotherapy treated group. There was evidence of heterogeneity between studies (P = 0.007), but no reason was found to explain the difference of effect in the studies included. See Analysis 1.5.

Sensitivity analysis was again performed for the Frew 2006 study by replacing the 100,000 SQ-U data included in the above meta-analysis with the data from the 10,000 SQ-U arm, to test the effect on the result. The revised combined SMD was -0.60 (95% CI -1.02 to -0.19, P < 0.004). Significant heterogeneity between studies was still evident (P < 0.04).

Of the ten studies not included in the meta-anlysis, eight favoured the intervention group. A description of data from these studies can be found in Table 5.

6. Ocular symptom scores

Three studies were included for ocular symptom score analysis, comprising active immunotherapy subjects n = 226 and placebo subjects n = 119 (Dolz 1996; Ferrer 2005; Frew 2006). The combined SMD for ocular symptom scores following subcutaneous immunotherapy was -1.80 (95% CI -3.28 to -0.31) (P < 0.02) indicating a significant reduction in ocular symptom scores in the immunotherapy treated group. There was evidence of heterogeneity between studies (P < 0.00001), but no reason was found to explain the difference of effect in the studies included. See Analysis 1.6.

Data obtained for this outcome were almost always non-normally distributed (skewed) and therefore many studies reported results as median values. Strenuous attempts were made to obtain mean (standard deviation) data direct from authors and values were only included after data were obtained. Leynadier 2001 provided mean values but not SD values as requested.

Sensitivity analysis was performed for the Frew 2006 study by replacing the 100,000 SQ-U data included in the above meta-analysis with the data from the 10,000 SQ-U arm, to test the effect on the result. The revised combined SMD was -1.80 (95% CI -3.33 to -0.27) (P < 0.02). Significant heterogeneity between studies was still evident (P < 0.00001).

Of the nine studies not included in the meta-analysis, six favoured the intervention group. A description of data from these studies can be found in Table 6.

7. Global improvement

Data obtained for this outcome were almost always non-normally distributed (skewed) and therefore many studies reported results as median values. Of the nine studies all favoured the intervention group. A description of data from these studies can be found in Table 7.

8. Rhinoconjunctivitis quality of life

Five studies were included in the rhinoconjunctivitis quality of life meta-analysis, comprising active immunotherapy subjects n = 332 and placebo subjects n = 239 (Corrigan 2005; Ferrer 2005; Frew 2006; Jutel 2005; Walker 2001). The combined SMD for rhinoconjunctivitis quality of life following subcutaneous immunotherapy was -0.52 (95% CI -0.69 to -0.34, P < 0.00001) indicating a clinically and statistically significant improvement in rhinoconjunctivitis quality of life in the immunotherapy treated group. There was no evidence of heterogeneity between studies (P = 0.50). See Analysis 1.9.

Sensitivity analysis was performed for the Frew 2006 study by replacing the 100,000 SQ-U data included in the above meta-analysis with the data from the 10,000 SQ-U arm, to test the effect on the result. The revised combined SMD was -0.39 (95% CI -0.57 to 0.21, P < 0.0001). Again there was no evidence of heterogeneity between studies (P = 0.74).

In the Alvarez-Cuesta 2005 study, during the pollen season, immunotherapy treated patients had significantly greater improvements both in overall (Rhinitis Quality of Life Questionnaire (RQLQ)) and in five of the seven Health-Related Quality of Life (HRQL) domains (sleep, non-hayfever symptoms, practical problems, nasal symptoms and eye symptoms). These differences also reached, or surpassed, the proposed threshold of clinical relevance (> 0.5 U) for total score and the five domains, including practical problems. Overall quality of life mean (95% CI) was 1.74 (1.50 to 1.98) for the immunotherapy group and 2.34 (1.87 to 2.81) for the placebo group (P < 0.05). Although mean values were given, no SD was provided therefore it was not possible to include this study in the meta-analysis.

9. Adverse events

Adverse events were searched for in all studies included in this review. Comparisons were made between subjects treated with subcutaneous allergen specific immunotherapy and subjects treated with placebo control. Adverse events were analysed as local or systemic reactions. Local reactions were analysed in two subgroups according to their need for treatment. Systemic reactions were analysed according to their severity (grading system) and time of onset (before or after 30 minutes) as described above.

The following paragraphs and data provide an overview of the adverse events reported in the included studies. Combining these can be problematic. Ideally a formal meta-analysis would be undertaken. However, most studies reported number of adverse events, rather than the number of participants in which one or more adverse events were observed, making such an analysis difficult. Although it might appear both clinically appropriate and mathematically simple to add up the number of events and divide this by the number of injections or participants (and we do indeed present some of these data) there is a danger that such pooling may undermine the effects of the randomisation process in the individual trials. As a result these data should be considered with some caution.

9.1 Local reaction

Thirty studies reported local reactions in their outcomes, which comprised n = 999 active immunotherapy subjects and n = 697 placebo subjects (Alvarez-Cuesta 2005; Arvidsson 2002; Armentia-Medina 1989; Balda 1998; Bodtger 2002; Bousquet 1990; Brunet 1992a; Corrigan 2005; D'Amato 1995; Dolz 1996; Drachenberg 2001; Durham 1999; Ferrer 2005; Frew 2006; Grammer 1982; Grammer 1983; Grammer 1984a; Grammer 1986; Grammer 1987; Jutel 2005; Karmaker 1994; Lee 1982; Leynadier 2001; Meriney 1986; Ortolani 1984; Ortolani 1994; Pastorello 1992; Tari 1997; Walker 2001; Zenner 1997).

9.1.1 Local reaction not requiring treatment

Twenty-four studies reported local reactions not requiring treatment; 834 events were reported in the immunotherapy treated group (92%, number of participants = 907) and 227 events in the placebo group (33%, number of participants = 697) (Alvarez-Cuesta 2005; Armentia-Medina 1989; Balda 1998; Bodtger 2002; Bousquet 1990; Brunet 1992a; Corrigan 2005; D'Amato 1995; Drachenberg 2001; Ferrer 2005; Frew 2006; Grammer 1982; Grammer 1983; Grammer 1984a; Grammer 1986; Grammer 1987; Jutel 2005; Karmaker 1994; Lee 1982; Leynadier 2001; Meriney 1986; Ortolani 1984; Ortolani 1994; Zenner 1997).

9.1.2 Local reaction requiring treatment

Seven studies reported local reactions requiring treatment; 21 events were reported in the immunotherapy treated group (10%, number of participants = 208) and eight events in the placebo group (4%, number of participants = 186) (Balda 1998; Bodtger 2002; D'Amato 1995; Dolz 1996; Grammer 1983; Lee 1982; Zenner 1997).

9.2 Systemic reaction

Thirty-three studies reported systemic reactions in their outcomes; n = 1051 active immunotherapy subjects and n = 857 placebo subjects (Alvarez-Cuesta 2005; Armentia-Medina 1989; Arvidsson 2002; Balda 1998; Bodtger 2002; Bousquet 1987a; Bousquet 1987b; Bousquet 1990; Corrigan 2005; D'Amato 1995; Dolz 1996; Drachenberg 2001; Durham 1999; Ferrer 2005; Fling 1989; Frew 2006; Grammer 1982; Grammer 1983; Grammer 1984a; Grammer 1986; Grammer 1987; Iliopoulos 1991; Jutel 2005; Leynadier 2001; Meriney 1986; Metzger 1981; Mirone 2004; Ortolani 1984; Ortolani 1994; Pastorello 1992; Tari 1997; Walker 2001; Zenner 1997).

9.2.1 Early systemic reaction grade 2 (< 30 minutes)

Seventeen studies reported early systemic reactions grade 2 (<30 minutes) in their outcomes (Alvarez-Cuesta 2005; Armentia-Medina 1989; Arvidsson 2002; Balda 1998; Bodtger 2002; Corrigan 2005; Dolz 1996; Drachenberg 2001; Ferrer 2005; Frew 2006; Iliopoulos 1991; Jutel 2005; Leynadier 2001; Mirone 2004; Ortolani 1994; Tari 1997; Zenner 1997); 154 events were reported in the immunotherapy treated group (22%, number of participants = 706) and 44 events in the placebo group (8%, number of participants = 566).

9.2.2 Early systemic reaction grade 3 (< 30 minutes)

Thirteen studies reported early systemic reactions grade 3 (<30 minutes) in their outcomes (Alvarez-Cuesta 2005; Armentia-Medina 1989; Balda 1998; Bousquet 1987a; Bousquet 1987b; Corrigan 2005; Ferrer 2005; Frew 2006; Jutel 2005; Leynadier 2001; Metzger 1981; Ortolani 1994; Zenner 1997); 43 events were reported in the immunotherapy treated group (7%, number of participants = 615) and three events in the placebo group (0.65%, number of participants = 463).

9.2.3 Early systemic reaction grade 4 (< 30 minutes)

Nine studies reported early systemic reactions grade 4 (<30 minutes) in their outcomes (Alvarez-Cuesta 2005; Armentia-Medina 1989; Corrigan 2005; Ferrer 2005; Fling 1989; Frew 2006; Jutel 2005; Mirone 2004; Ortolani 1994); three events were reported in the immunotherapy treated group (0.72%, number of participants = 417) and one event in the placebo group (0.33%, number of participants = 303).

9.2.4 Late systemic reaction (> 30 minutes)

Eleven studies reported late systemic reactions (> 30 minutes) in their outcomes (Balda 1998; Bodtger 2002; Bousquet 1990; Corrigan 2005; Ferrer 2005; Frew 2006; Jutel 2005; Ortolani 1994; Pastorello 1992; Walker 2001; Zenner 1997); 458 events were reported in the immunotherapy treated group (89%, number of participants = 514) and 148 events in the placebo group (36%, number of participants = 412).

9.2.5 - Systemic reaction - severity and time of onset not specified

Three studies reported systemic reactions with the severity not specified in their outcomes (Bousquet 1991; Karmaker 1994; Lee 1982); 12 events were reported in the immunotherapy treated group (8.5%, number of participants = 142) and no events in the placebo group (number of participants = 63).

10. Adrenaline use

Thirteen studies reported use of adrenaline (Alvarez-Cuesta 2005; Corrigan 2005; Dolz 1996; Bousquet 1987a; Bousquet 1987b; Ferrer 2005; Fling 1989; Frew 2006; Iliopoulos 1991; Jutel 2005; Metzger 1981; Mirone 2004; Ortolani 1994); 19 events were reported in the immunotherapy treated group (0.13%, number of injections given = 14,085) and 1 event in the placebo group (0.01%, number of injections given = 8278) (see Figure 1).

Figure 1.

Adrenaline use (in 13 studies)

Active			Placebo		
Adrenaline use	Participants (%)	Injections (%)	Adrenaline use	Participants (%)	Injections (%)
19	557 (3.41)	14,085 (0.13)	1	404 (0.25)	8,278 (0.01)

11. Cost

Not a single study included assessment of cost.

12. Serum antibody levels

12.1 Specific IgG

Twenty-eight studies measured changes in specific IgG (Armentia-Medina 1989; Bousquet 1987a; Bousquet 1987b; Bousquet 1988; Bousquet 1989; Bousquet 1990; Bousquet 1991; Brewczynski 1999; Brunet 1992a; Dolz 1996; Drachenberg 2001; Fling 1989; Grammer 1982; Grammer 1983; Grammer 1986; Grammer 1987; Iliopoulos 1991; Juniper 1985; Karmaker 1994; Litwin 1991; Meriney 1986; Metzger 1981; Norman 1982; Ortolani 1984; Ortolani 1994; Pastorello 1992; Tari 1997). All studies reported a significant increase in specific IgG levels after treatment with specific immunotherapy compared with placebo.

Of these, only four studies provided suitable data for meta-analysis (Drachenberg 2001; Ortolani 1984; Ortolani 1994; Pastorello 1992); which comprised active immunotherapy subjects n = 107 and placebo subjects n = 84. The combined SMD was 1.90 (95% CI 0.88 to 2.93 (P = 0.0003)) indicating a significant increase of specific IgG in the immunotherapy treated group. There was evidence of heterogeneity between studies (P = 0.001), but no reason was found to explain the difference of effect in the studies included. See Analysis 1.7.

Description of data from studies not included in the meta-analysis is presented in Table 8.

12.2 Specific IgG4

Eleven studies measured changes in specific IgG4 (Ariano 1999; Balda 1998; Brewczynski 1999; Dolz 1996; Fling 1989; Leynadier 2001; Ortolani 1984; Ortolani 1994; Pastorello 1992; Tari 1997; Zenner 1997). All studies, except one (Fling 1989) reported a significant increase in specific IgG4 levels after treatment with specific immunotherapy compared with placebo.

Of these, only five studies provided suitable data for meta-analysis (Balda 1998; Corrigan 2005; Dolz 1996; Jutel 2005; Zenner 1997), comprising active immunotherapy subjects n = 206 and placebo subjects n = 198. The combined SMD was 0.79 (95% CI 0.49 to 1.08 (P < 0.00001)) indicating a significant increase of specific IgG4 in the immunotherapy treated group. There was no evidence of heterogeneity between studies (P = 0.14). See Analysis 1.8.

Description of data from studies not included in the meta-analysis is presented in Table 9.

12.3 Specific IgE

Thirty studies measured changes in allergen specific IgE; of these, 20 studies reported an increase in specific IgE levels (Ariano 1999; Armentia-Medina 1989; Bousquet 1987a; Bousquet 1988; Bousquet 1989; Bousquet 1990; Brunet 1992a; Grammer 1986; Grammer 1987; Iliopoulos 1991; Juniper 1985; Karmaker 1994; Lee 1982; Leynadier 2001; Litwin 1991; Metzger 1981; Norman 1982; Pastorello 1992; Zenner 1997).

Nine studies reported no changes in these levels (Balda 1998; Bodtger 2002; Brewczynski 1999; Dolz 1996; Drachenberg 2001; Meriney 1986; Ortolani 1984; Ortolani 1994; Tari 1997). One study (Fling 1989) reported a reduction of specific IgE levels measured during the pollen season after immunotherapy.

Data were not suitable for meta-analysis, therefore, description of data from studies is presented in Table 10.

13.Specific allergen challenges

13.1 Nasal challenge

Thirteen studies performed nasal challenges (Bodtger 2002; Bousquet 1987b; Bousquet 1988; Bousquet 1990; Bousquet 1991; Brunet 1992a; D'Amato 1995; Iliopoulos 1991; Leynadier 2001; Ortolani 1994; Pastorello 1992; Tari 1997). Most of the studies showed an increase in the allergen provocation dose for the active treatment group.

Data were not suitable for meta-analysis, therefore, description of data from studies is presented in Table 11.

13.2 Conjunctival challenge

Six studies performed conjunctival challenges; of these, four studies (Dolz 1996; Durham 1999; Ortolani 1994; Varney 1991) showed an increased in the conjunctival threshold dose of allergen after immunotherapy. Two studies showed no differences in both groups (Arvidsson 2002; Bodtger 2002).

Data were not suitable for meta-analysis, therefore description of data from studies is presented in Table 12.

13.3 Skin challenge

Twenty-one studies performed skin challenges (Ariano 1999; Armentia-Medina 1989; Bodtger 2002; Bousquet 1987a; Bousquet 1988; Bousquet 1989; Bousquet 1990; Bousquet 1991; D'Amato 1995 ; Dolz 1996; Drachenberg 2001; Durham 1999; Fling 1989; Iliopoulos 1991; Leynadier 2001; Ortolani 1994; Pastorello 1992; Tari 1997; Varney 1991; Walker 2001; Zenner 1997). All studies reported a reduction in the skin reactivity after immunotherapy.

Data were not suitable for meta-analysis, therefore description of data from studies is presented in Table 13.

13.4 Bronchial challenge

Three studies performed bronchial challenges (Armentia-Medina 1989; Dolz 1996; Ortolani 1984). Data were not suitable for meta-analysis, therefore description of data from studies is presented in Table 14.

14. Deaths

No fatal events were reported in any of the studies included in this systematic review.

DISCUSSION

We have performed a comprehensive systematic review of the effectiveness of subcutaneous injection specific allergen immunotherapy in patients with seasonal allergic rhinitis.

This systematic review found 51 randomised controlled trials which satisfied our inclusion criteria. Symptom scores were described as significantly reduced in 31 studies and medication scores were also described as significantly reduced in 24 studies. However, symptom score data from only 15 studies and medication score data from

only 13 studies were suitable for meta-analyses. These studies were identified through an extensive search of the published and unpublished literature and this review therefore represents, we believe, a state of the art and up-to-date synthesis of the best evidence available (up to February 2006) on the efficacy and safety of injection specific allergen immunotherapy in patients with seasonal allergic rhinitis.

A degree of caution in interpretation of these data is required as there was significant heterogeneity between studies which maybe due to the wide variety of scoring systems used across studies. This is in part compensated for by use of the standardised mean difference in the analyses. Furthermore, it is difficult to know what constitutes a clinically important difference on these scales; the range of symptom scores used potentially also threatens the appropriateness of combining data in a meta-analysis. The variability in the effect of specific injection immunotherapy may be also explained by variable responses to treatment according to the type of allergen used, the quality of allergen vaccines used, the age of participants included in these trials, or the dose and duration of treatment given. Also, in this review, we found a lack of information in some of the studies in describing the optimal maintenance dose of major allergen; this is important to consider because studies suggest that therapeutic efficacy may require high allergen doses. (Low dose immunotherapy is usually ineffective (WHO 1998), therefore therapeutic efficacy correlates with an optimal maintenance dose in the range of 5 to 20 mcg of major allergen per injection for a number of primary allergens).

The study also shows that the reported clinical benefits may translate into improvements in disease specific quality of life: the most recent studies have reported on outcomes using validated rhinitis quality of life questionnaires. Data relating to individual organ-specific symptom scores from a number of the studies also consistently point to the efficacy of immunotherapy (compared with placebo) in improving nasal, ocular and global symptom scores in patients with seasonal allergic rhinitis.

In addition, these trials have found strong and consistent evidence that immunotherapy results in favourable responses in a number of immunological outcomes, and although these data are of interest in terms of understanding the pathophysiology of the underlying disease process and the mechanisms of action of injection immunotherapy, their clinical significance remains unclear. The data raise the question whether such biomarkers may be surrogate and/or predictive of the clinical response to immunotherapy and therefore useful for monitoring immunotherapy. Larger controlled trials are required to test this possibility. Data on the cost-effectiveness of injection specific allergen immunotherapy represent an important omission in the reported trials and this data gap needs to be filled by future studies.

In this systematic review, there were no accepted studies of allergen injection immunotherapy that were conducted exclusively in children. Furthermore only nine studies extended the age range to participants younger than 18 years of age; one study included patients between 6 and 56 years of age (Karmaker 1994); however, no data assessing specific outcomes were reported in the younger participants.

We have found that patients treated with injection immunotherapy are at increased risk of both local and systemic adverse reactions. In the majority of cases, symptoms were readily reversible with appropriate treatment. This review shows that four events were categorized as 'early systemic reaction grade 4'; three reactions were described in the active treatment group (two cases of anaphylaxis and one case of exacerbation of asthma with oedema of glottis and hypotension) and one case in the placebo group (described as anaphylaxis). No further explanation was given regarding the clinical characteristics of these individuals. It was reported that all subjects fully recovered after adequate treatment and it is relevant that all continued with immunotherapy and none dropped out following these reactions. The number of participants involved in the trials varies from 18 to 410. These numbers compare well with guidelines for Phase I, ll and III clinical trials and provide useful information on the safety of the procedure under carefully controlled circumstances.

Although fatalities associated with the use of immunotherapy have been previously reported in the medical literature (CSM 1986; Reid 1993; Bernstein 2004; Aaronson 2004), these occurred almost exclusively in patients with co-existing asthma (16 of 17 in the CSM report). Furthermore, asthma was frequently poorly controlled (i.e. lability, required steroids, and/or prior hospitalisations) and there were additional risk factors. In the AAAAI report (Reid 1993), hay fever was reported in 53% (9 of 17) of the patients who died; eight of these patients had coexisting asthma, some also had diabetes and coronary vascular disease. Only one patient was reported to have had hay fever only, but he had coexisting hypertension, cardiovascular disease, and was receiving a B-blocker treatment. Delay or omission in the use of adrenaline in anaphylaxis, wrong selection of candidates for injection immunotherapy, dosing errors, no cardiorespiratory resuscitation facilities available and no adherence to immunotherapy practice guidelines can be responsible for these fatalities.

In the 13 out of 52 studies that reported that adrenaline was available for use, it was only given in seven of these 13 studies. In the seven studies where adrenaline was administered, there were 19 events in the active group and one event in the placebo group that were treated with this medication; this correspond to 0.13% of the 14,085 injections given in the active group and 0.01% of 8278 injections given in the placebo group (Figure 01). These data are likely to overestimate adrenaline usage since it is probable that in the majority of the 39 studies where adrenaline was not mentioned it is unlikely that it was used.

The reasons for adrenaline use varied; these include nasal and ocular itching, facial reddening, pharyngeal itching with cough, moderate wheezing, urticaria, angioedema. In three cases anaphylaxis was reported as the inciting event, although precise details not given. In some studies (Iliopoulos 1991 and Dolz 1996), adrenaline was given as a 'first choice' treatment and adverse events were not described as anaphylaxis. In many instances adrenaline appeared to have been given as a precautionary treatment and should not be regarded as a marker 'per se' of anaphylaxis. In the large multicentre study by Frew 2006 which included 307 subjects on active immunotherapy, and in whom full documentation of both early and delayed side effects were recorded in patient diary cards, there was no recorded use of adrenaline.

In conclusion, we have found that specific allergen injection immunotherapy is a safe and efficacious treatment in reducing symptom severity and the requirement for anti-allergic medication. Evaluating the clinical benefits of immunotherapy treatment and

the tolerable nature of side effects, we can consider that the risk/benefit ratio of injection immunotherapy favours treating patients with seasonal allergic rhinitis who have not responded to standard drugs, provided that potential risks and benefits are properly assessed and explained to the patient. In view of the occasional occurrence of systemic side effects following injections and the reported use of adrenaline to treat such reactions, it is important that injection immunotherapy is performed in the immediate presence of a physician and administered by personnel that are fully trained and who are experienced in the early recognition and treatment of such reactions.

AUTHORS' CONCLUSIONS

Implications for practice

Injection immunotherapy for grass pollen is effective in improving symptoms and reducing the need for medication in patients with seasonal allergic rhinitis and improves disease specific quality of life in these subjects. Whether the treatment is cost-effective remains to be determined.

There are significant risks associated with the use of injection immunotherapy including the rare occurrence of adverse events requiring adrenaline, but when administered in controlled clinical settings this risk is greatly reduced.

In summary, we conclude that injection immunotherapy is a safe and valid treatment option in patients with seasonal allergic rhinitis. It is particularly useful in those who fail to respond adequately to other treatments, provided that it is administered in settings in which patients can be monitored and, if necessary, promptly and effectively treated for systemic allergic reactions.

Implications for research

There is a need for studies to report trial procedures more clearly as detailed in the CONSORT (Junker 1996) statements and in particular to describe the randomisation technique employed. Validated outcome measures should be used wherever possible taking care to distinguish between statistical and clinical significance. Given the known risks, all trials should more explicitly record and publish information on adverse events. Finally, there is a pressing need for cost-effectiveness studies for what is a resource intensive intervention.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alvarez-Cuesta 2005

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Spain. Inclusion criteria: moderate SAR (+), SPT (+) and CAP (+) to grass pollen (Dactylis glomerata and Olea europea). No previous SIT. Total n = 57. Active n = 25 (12m). Placebo n = 28 (16m). Age range 18-58 years. Five mild asthmatics (2 in active group) were included.
Interventions	Treatment: standardised depigmented, polymerised extract (Lab LETI, S.L.). The median accumulated dose of D. glomerata was 1.48 mg (IQ range 1.44-2.83) and 1.66 mg (1.52-3.06) of Olea europea. Duration: 3 years (2 years as a pre-treatment monitoring period and 1 year as a treatment period - placebo or SIT).
Outcomes	Symptom/medication scores recorded by patients during the pollen season. RQLQ. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ariano 1999

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Italy.

Ariano 1999 *(Continued)*

	Inclusion criteria: all patients had single sensitisation to Parietaria grass pollen; SPT(++) and RAST (> class 2). Clinical symptoms for at least 2 years. Total n = 25; active group n = 13 (4m), placebo group n = 12 (4m). Age range 13-62 years. Five patients had mild intermittent asthma.
Interventions	Treatment: Parietaria judaica pollen/allergoid. Pre-seasonal dose given. Treatment was given for 3 years. Up-dosing: 1000, 2000, 4000, 6000, 8000, 10000, AUeq each week. Maintenance dose was 10000 AUeq monthly.
Outcomes	Symptoms/medication scores recorded by patient in diary cards during pollen seasons (March-October). Global assessment. Adverse reactions. Skin reactivity by a standardised SPT at baseline and during year 3 of study. Allergen-specific IgG4 and IgE. Pollen counts.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Armentia-Medina 1989

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Spain. Inclusion criteria: SAR(+) and SPT(+) to Bermuda grass pollen (BGP). Total n = 30; active group n = 19, placebo group n = 11. No distribution by sex reported. 21 patients had history of asthma. Aged 12-55 years.
Interventions	Rush IT protocol with Bermuda grass pollen. 17 total injections given. Pre-seasonal (Oct-Nov). Duration of treatment was 4 days. Max dosage was 60 BU.
Outcomes	Patient symptoms assessed using a grade system (0-4 scale). SPT by conventional prick test and the end point titration technique. Non-specific bronchial hyperreactivity test with BGP.

Armentia-Medina 1989 *(Continued)*

	Adverse reactions. Specific IgE and IgG to BGP.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Arvidsson 2002

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Sweden. Inclusion criteria: SAR(+) +/- seasonal asthma, SPT(+), RAST(+) and conjunctival provocation test (+) to birch pollen. Total n = 49; active group n = 24 (9m, 9 asthmatics), placebo group n = 25 (11m, 9 asthmatics). Aged 19-45 years.
Interventions	Treatment: Alutard SQ Betula verrucosa (birch pollen) allergen extract aluminum hydroxide-adsorbed. Duration was 2 years after reaching maintenance. Initial concentration of 100 SQ-U/ml and a maximum concentration of 100,000 SQ-U/ml.
Outcomes	Symptoms/medication scores reported by patients in diary cards. Adverse events. Skin and conjunctival provocation test to birch pollen. Pollen counts. Bronchial Sx scores.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Balda 1998

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Germany. Multicentre study: 14 University Allergy Departments.

Balda 1998 *(Continued)*

	Inclusion criteria: SAR(+), SPT(+) CPT(+) and RAST(+) to alder, hazel or birch pollen. Total n = 111; active group n = 51 (23m) and placebo n = 60 (25m). Age range 18 to 58. > 50% patients asthma.
Interventions	Treatment: tree pollen allergen extract of Carylus avellana, Alnus glutinosa and Betula verrucosa for 7 weeks before the beginning of the tree-pollen season. Concentration of 10, 100 and 1000 SE/ml.
Outcomes	Symptoms/medication scores recorded by patients. Nasal, bronchial symptoms. Global assessment. Adverse reactions. Skin sensitivity. Specific IgE and IgG4. Eosinophil cationic protein.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bodtger 2002

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Denmark. Inclusion criteria: SAR (+) +/- seasonal asthma, SPT(+) and RAST (+) to birch pollen. Total n = 35; active group n = 17 (7m, 7 asthmatics), placebo group n = 18 (7m, 7 asthmatics). Aged 19-46 years.
Interventions	Treatment: Alutard SQ Betula verrucosa (birch pollen) allergen extract aluminum hydroxide-adsorbed. Clustered-injection schedule with an initial concentration of 10 SQ-U/ml and a maximum concentration of 100,000 SQ-U/ml. Duration was 10 months.
Outcomes	Symptom/medication scores reported by patients in diary cards. Adverse events. Sensitivity to allergen provocation in skin, conjunctiva and nasal mucosa was measured before and after 10 months of treatment. Total and specific IgE.

Bodtger 2002 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bousquet 1987a

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: France and Germany. Inclusion criteria: SAR(+) +/- asthma(+) +/- conjunctivitis(+), SPT (+) and RAST (> class 3-4) to Orchard grass pollen. Total n = 45; grass pollen extract group n = 15, allergoid group n = 19 and placebo group n = 11. No distribution by sex reported. More than 50% patients had asthma +/- conjunctivitis.
Interventions	Treatment: standardised orchard grass-pollen extract, six-mixed grass-pollen allergoid. Rush IT protocol used for 4 days. Pre-seasonal. 9 injections given with pollen extract and 10 injections given with allergoid. Max dosage: 2 IR pollen extract and 1000 PNU allergoid.
Outcomes	Patient symptoms score recorded in diary cards. Skin test titration. Adverse events. Serum orchard grass-pollen IgE and IgG. Pollen counts.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bousquet 1987b

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: France. Inclusion criteria: patients with severe SAR to orchard grass pollen. Total n = 59; active group n = 39, placebo group n = 20. No distribution by sex reported.

Bousquet 1987b *(Continued)*

	Adults.
Interventions	Treatment: High-molecular weight formalinised allergoid with orchard grass pollen. Injections n = 9, given pre-seasonally. Dosage used 5,695 to 73,800 PNU.
Outcomes	Symptoms recorded by patients. Adverse events. Nasal provocation test before and after IT. Serum grass pollen IgG.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bousquet 1988

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: France and Germany. Inclusion criteria: patients with severe SAR to orchard grass pollen. SPT(+) and RAST(+) to orchard grass pollen. Total n = 25; active group n = 15, placebo group n = 10. 15 males. Adults.
Interventions	Treatment: High-molecular weight formalinised allergoid with orchard grass pollen. Injections n = 9, given pre-seasonally. Initial dose 50 PNU last dose 2000 PNU.
Outcomes	Symptoms recorded by patients. Nasal provocation test before and after IT. SPT to orchard extracts. Serum grass pollen IgG and IgE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bousquet 1989

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: France and Germany. Inclusion criteria: patients with severe SAR to orchard grass pollen. SPT(+) and RAST(+) to orchard grass pollen. Total n = 60; GOID group n = 15, HMW-GOID group n = 13, standardised extract group n = 18, placebo group n = 14. Adults. Some patients were asthmatics.
Interventions	Treatment: High-molecular weight formalinised allergoid (HMW-GOID) with orchard grass pollen and HMG-fractionated by gel filtration (molecules >85,000 daltons, GOID). Injections n = 9, given pre-seasonally. Initial dose 50 PNU last dose 2000 PNU.
Outcomes	Symptoms recorded by patients. SPT to orchard extracts. Adverse events recorded. Serum grass pollen IgG and IgE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bousquet 1990

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: France. Inclusion criteria: patients with severe SAR to orchard grass pollen. SPT(+) and RAST(+) to orchard grass pollen. Total n = 57; high dosage group n = 20, low dosage group n = 19, placebo group n = 18. Adults, 24 males. Some patients were asthmatics.
Interventions	Treatment: High-molecular weight formalinised allergoid with orchard grass pollen. Two groups: high dose schedule with a maximal dose of 10,000 PNU and a low-dose schedule with a maximal dose of 2,000 PNU. 10 injections were given pre-seasonally. Initial dose 100 PNU.
Outcomes	Symptoms recorded by patients. Medication scores. SPT and NPT to orchard extracts.

Bousquet 1990 *(Continued)*

	Adverse events recorded. Serum grass pollen IgG and IgE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bousquet 1991

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: France and Germany. Inclusion criteria: patients with SAR symptoms (April - July), SPT (+) and RAST (+) to orchard grass pollen. No previous IT. Total n = 70; 36 patients allergic only to grass pollens received single-allergen (orchard grass pollen) extracts injections or placebo and 34 patients allergic to multiple-pollen species received mixed allergen extract injections or placebo. Aged 14 to 44 years. No sex distribution reported.
Interventions	Pre-seasonal treatment with standardised extracts from orchard grass were given for 3 days in up-dosing phase (max dosage 2000 BU). Maintenance dose of 2000 BU was administrated five times at weekly intervals.
Outcomes	Symptom/medication scores. Nasal challenges. Titration of mediators in nasal secretions. SPTs. Adverse reactions. Serum orchard grass pollen IgG and IgE. Pollen counts.
Notes	Multiple pollen extract results were excluded from this review. Patients received 1000 BU Orchard grass pollen extracts every 2 weeks during the pollen season.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Brewczynski 1999

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Germany. Inclusion criteria: patients with SAR symptoms, SPT(+) and RAST(+) to grass pollen. No previous IT. Total n = 20; active group n = 10 (4m), placebo group n = 10 (6m). Aged 14 to 34 years. Some patients were asthmatics.
Interventions	Treatment: modified extract (allergoid) was used. Pre-seasonal treatment given. Duration of treatment was 3 years. Cumulative dose was 120,000 AU per year.
Outcomes	Symptom/medication scores in diary cards. Adverse events. Grass pollen specific IgE and IgG antibody levels.
Notes	Paper was translated from German

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Brunet 1992a

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Canada. Inclusion criteria: clear-cut history SAR without asthma, SPT(+) and RAST(+) to ragweed. Total n = 40; active group n = 13 (10m), placebo group n = 14 (8m) and control group n = 13 (8m) . Aged 19 to 56 years.
Interventions	Treatment: Alum-precipitated aqueous ragweed extracts. Pres-seasonal dosage was given in 9 consecutive weeks (max 3000 PNU). Maintenance dose and duration was not reported.
Outcomes	Symptom/medication score recorded in dairy cards. Adverse events. Nasal challenge. Ragweed-induced basophil histamine release. Ragweed-specific IgE and IgG antibody levels.
Notes	A non-atopic volunteer group (n = 13, with negative SPT and RAST) were used as control group

Brunet 1992a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ceuppens 2004

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Belgium and the Netherlands. Inclusion criteria: Birch allergic mono-sensitised patients. Total n = 78. Active n = 39 (18m). Placebo = 39 (17m). 38 patients had mild-moderate seasonal asthma (16 in active group). Median age range was 45 yrs.
Interventions	Treatment: Glutaraldehyde-modified allergen extract from birch pollen adsorbed onto aluminium hydroxide (PURETHAL). Six injections given. Duration: 1 year.
Outcomes	Symptom/medication scores recorded by patients during the pollen season. Adverse events. Serum sIgE, sIgG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Charpin 2003

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: France. Inclusion criteria: Moderate to severe European cypress SAR Total n = 40. Active n = 22 (?m). Placebo = 18 (?m). Adults. No asthma data given.
Interventions	Treatment: standardised depot Juniperus ashei extract with a potency of 100 IR containing 54 ug Jun a1/ml (Alustal, Stallergenes). Two weekly injections (0.1 IR/ml) were given until reach maintenance dose of 0.3 ml of the 100 IR concentration.
Outcomes	Symptom/medication scores recorded by patients during the pollen season.

Charpin 2003 *(Continued)*

	Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Corrigan 2005

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: UK and Germany. Inclusion criteria: SAR (+), SPT (+) and CPT (+) to grass pollen. No SIT previous last 3 yrs. Total n = 154. Active n = 77 (35m). Placebo = 77 (29m). Age range 18-60 yrs. 42 mild-moderate asthmatics (19 in active group) were included.
Interventions	Treatment: Allergoid absorbed extracts of six grass pollen allergens (Holcus lantus, Dactylis glomerata, Lolium perenne, Phleum pratene, Poa pratensis, Festula pratensis) co-precipitated with aluminium hydroxide. Two concentrations used 1,000 TU/ml and 10,000 TU/ml (Allergovit, Allergopharma). Average number of injections was 9 per year. Median values of maximum study dose given was 6,000 TU. Duration was two consecutive pre-seasons.
Outcomes	Symptom/medication scores recorded by patients during the pollen season. RQLQ. CPT. Adverse events. sIgE, sIgG1 and sIgG4.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

D'Amato 1995

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Italy and USA. Inclusion criteria: history of rhinitis +/- asthma during the Parietaria pollen season with SPT(+), nasal provocation test (+) and RAST (> class2) to Parietaria.

D'Amato 1995 *(Continued)*

	Total n = 36; active group n = 19 (10m) and placebo group n = 17 (10m). Mean age range 28.6 (active) and 34.6 (placebo). Seven patients had asthma.
Interventions	Treatment: Alum adsorbed partially purified Parietaria extract. No up-dosing dosage and time-table reported. Targeted maintenance dose was 12,500 BU for 3 years.
Outcomes	Symptom/medication score recorded in diary cards using VAS. Adverse reactions. Nasal provocation tests. Skin test suppression. Global improvement. Pollen count.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dolz 1996

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Spain. Inclusion criteria: clinical history of SAR. SPT (+) CPT (+) and RAST(+) to grass pollen. Total n = 28; active group n = 18 and placebo n = 10. Age range 15 to 35 years. Six patients had mild seasonal asthma. No sex distribution given.
Interventions	Treatment: grass pollen allergen extract Allutard SQ aluminum hydroxide-adsorbed Phleum, Dactylis and Lolium for 3 years. Initial concentration of 100 USQ/ml and a maximum concentration of 100 000 USQ/ml.
Outcomes	Symptom/medication scores recorded by patients. Adverse reactions. Conjunctival, skin and bronchial provocation tests. Total serum IgE. Specific IgG
Notes	

Risk of bias

Dolz 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Drachenberg 2001

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Germany and Austria. Inclusion criteria: SAR(+), SPT(+) and RAST(+) to grasses and S. cereale. Total n = 124; active group n = 74 (40m, 32 asthmatics), placebo group n = 50 (23m, 25 asthmatics). Aged 18-60 years.
Interventions	Treatment: standardised allergy vaccine comprising a tyrosine-adsorbed glutaraldehyde-modified grass pollen extract containing nonophosphoryl lipid A (MPL). The vaccine contained a mixture of pollens from 12 temperate zone grasses (B2) and S. cereale (cultivated rye).
Outcomes	Symptom/medication scores. Adverse events. Titrated SPT. Specific IgG and IgE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Drachenberg 2002

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Germany. Inclusion criteria: SAR(+), conjunctivitis +/- asthma sensitised to birch, alder, hazel pollen. Total n = 84; active group n = 54 , placebo group n = 27. Aged 18-61 years.
Interventions	Treatment: The active group received 4 injections of L-tyrosine-adsrobed tree pollen allergoids plus 50 micrograms/mL monophosphoryl-lypid-A (MPL). Placebo injections consisted of L-tyrosine-solution (2%) in excipient solution.
Outcomes	Combined symptom/medication scores. Changes in skin reactivity (titrated SPT).

Drachenberg 2002 *(Continued)*

	Adverse events. Specific IgG and IgE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ferrer 2005

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Spain. Inclusion criteria: SAR (+) and SPT (+) to Parietaria judaica. Total n = 57. Active n = 28 (11m). Placebo = 29 (15m). Age range 15-55 yrs. 23 patients had mild-moderate seasonal asthma (13 in active group).
Interventions	Treatment: Parietaria judaica extract 25 BU/ml (1.5 ug/ml Par j 1), Pangramin Depot, ALK-Abello. Mean number of injections for each patient was 29.3±6.2. All patients in active group reached the predetermined maintenance dose of 29 BU. Duration: 20 months.
Outcomes	Symptom/medication scores recorded by patients during the pollen season. Adverse events. RQLQ. Immediate and late cutaneous response.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Fling 1989

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: typical history of SAR and SPT (+4) to mountain cedar pollen. Total n = 19; active group n = 12 (2m) and placebo group n = 7 (3m).

Fling 1989 *(Continued)*

	Aged 18-70 years.
Interventions	Treatment: Conventional IT with mountain cedar antigen beginning at a 1:100,000 wt/vol dilution and progressing by 0.05 ml increments until 0.5 ml was achieved. Then, a 10-fold higher concentration was given in the same dosing increments until maintenance was reached at 0.5 ml of 1:100 wt/vol or the highest tolerated dose.
Outcomes	Patient symptom/medication scores. Adverse events. Cutaneous (early and late reactions). Allergen-specific IgE, IgG. IgG1 and IgG4. Pollen counts.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Frew 2006

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: UK. Inclusion criteria: SAR (+) inadequately controlled with standard medication. SPT (+) and CAP (+) > class 2 to Phleum pratense. No SIT previous 5 yrs. Total n = 410. Active group 100,000 SQ-U n = 203 (110m), 10,000 SQ-U n = 104 (59m). Placebo group n = 103 (62m). Age range:18-60 yrs. Mild-moderate seasonal asthmatics were included.
Interventions	Treatment: standardised depot preparations of grass pollen extract (Alutard SQ-U Phleum pratense, ALK-Abello) were given by subcutaneous injection. The up-dosing phase consisted of 15 injections over 8 weeks. At each visit, 8 mg Acrivastine was given 15 mins before first injection, second injection was given 30 mins later. Maintenance injections given 6±2 weeks. Duration: 1 year
Outcomes	Symptom/medication scores recorded by patients during the pollen season. Nasal, eye and lung symptoms were recorded. Global assessment. Rhinoconjunctivitis RQLQ. Adverse events
Notes	Alutard Phleum pratense 100,000 SQ-U (ALK-Abello) corresponds to 20 µg of major allergen Phl p 5.

Frew 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Grammer 1982

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: SAR(+) and SPT(+4) to ragweed. Total n = 40; active group n = 21 and placebo n = 19. Aged 21-65 years. No sex distribution given.
Interventions	Treatment: Polymerised ragweed. Pre-seasonal treatment given. Duration of treatment was 15 weeks, one injection weekly. Max dosage given was 6250 PNU per injection.
Outcomes	Patient symptom score. Adverse events. Total serum antibody against ragweed antigen E.
Notes	Additional control group (n = 15) received no injections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Grammer 1983

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: SAR(+) and SPT(+4) to grass pollen. Total n = 26; active group n = 13 and placebo n = 13. Aged 21-65 years. No sex distribution given.
Interventions	Treatment: Polymerised grass extracts of rye, timothy, redtop, June, orchard and Bermuda. In 12 weekly injections the active group received approximately 48,000 PNU.

Grammer 1983 *(Continued)*

Outcomes	Patient symptom/medication score. Adverse events. Specific IgE. Pollen count.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Grammer 1984a

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: SAR(+) and SPT(4+) to ragweed. Total n = 42; active group n = 21 and placebo n = 21. Aged 21-65 years. No sex distribution given.
Interventions	Treatment: Polymerised ragweed. Pre-seasonal treatment given. Dosage schedule was a series of 4 weekly injections. No max dosage and time reported.
Outcomes	Patient symptom/medication score. Adverse events. Total serum antibody against ragweed antigen E.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Grammer 1984b

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: SAR(+) and SPT (+) to ragweed. Total n = 50; active group n = 19 (13m) and placebo n = 31 (23m).

Grammer 1984b *(Continued)*

	Asthmatics n = 8 in active group and n = 15 in placebo group.
Interventions	Treatment: Polymerised ragweed. In 15 weekly injections the active group received 50,000 PNU of ragweed, equivalent to 1200 mcg antigen. No max dose and timetable reported.
Outcomes	Patient symptom/medication score. Adverse events. Total serum antibody against ragweed antigen E.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Grammer 1986

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: SAR(+) and SPT(+) to either timothy, orchard or Bermuda grass pollen. Patients were paired on the basis of cutaneous end point titrations to timothy, orchard and Bermuda grass pollen extracts. Total n = 44; n = 15 received 3 grasses, n = 4 received 2 grasses and n = 1 received one grass. Placebo group n = 20.
Interventions	Treatment: individually polymerised grass immunotherapy with an accelerated dosage schedule. Duration: 9 weekly visits with 13 injections that totalled 24,000 PNU of each grass to which the patient had cutaneous reactivity.
Outcomes	Patient symptom/medication score. Adverse events. Specific serum IgE and IgG. Pollen count.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Grammer 1987

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: typical history of SAR to ragweed. Must had at least 30 mm sum of erythema to prick testing with 100,000 AU/ml ragweed extracts. Aged 21 to 60. Total n = 81; active group n = 36 and placebo n = 37. Sex distribution no reported. Asthmatics n = 12.
Interventions	Treatment: Polymerised ragweed. Patients received 15 injections in 15 weekly visits. No max dose and timetable reported.
Outcomes	Patient symptom/medication score. Adverse events. IgE and IgE antibody against ragweed levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Hauser 1995

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Germany. Inclusion criteria: patients with SAR symptoms, SPT(+) and RAST(+) to grass pollen. No previous IT. Total n = 21; active group n = 14, placebo group n = 7. No sex distribution given. Adults. Some patients were asthmatics.
Interventions	Treatment: 6 grass pollen mixture in depot form was used. Pre-seasonal treatment given. Duration of treatment was 6 months. Cumulative dose was 5,000 TE.
Outcomes	Symptom/medication scores in diary cards. Nasal allergen challenge. Number of eosinophils and IgE-positive cells in nasal mucosa.
Notes	Paper was translated from German.

Risk of bias

Hauser 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hauser 1997

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Germany Inclusion criteria: SAR (+) and SPT (+) to grass pollen. No SIT previous 5 years. Total n = 34. Active n = 17 (?m). Placebo = 17 (?m). Age range: 18-50 yrs. Mild-moderate asthmatics were included.
Interventions	Treatment: Alum-adsorbed grass allergoid (Allergovit, Allergopharma).Two strengths were used, 1000 and 10,000 TU/ml. 8 injections were given as an average per patient. Maximum dose was 6000 TU and the mean total cumulative dose was 15,012 TU).
Outcomes	Symptom scores. Serum sIgG. Nasal lavages and cytokine measurements (IL-1b, IL-4, IL-5, IL-6 and IL-8).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Iliopoulos 1991

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: clinical symptoms of SAR and SPT(+) to ragweed. Total n = 55, active group n = 21, placebo group n = 20, 14 patients dropped out before randomisation. No age or sex distribution reported.
Interventions	Treatment: short ragweed extract. Up-dosing weekly injections for 3 months, pre-seasonal. The maintenance dose was equivalent to 1.92 mcg of antigen, given bi-weekly for 9 months. Each treated patient received a total dose of approx 24 mcg of antigen extract.
Outcomes	Patient symptom/medication scores. Adverse reactions.

Iliopoulos 1991 *(Continued)*

	Nasal challenges and intradermal skin test (early and late reactions). Specific IgE and IgG antibodies.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Juniper 1985

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Canada. Inclusion criteria: clinical symptoms of SAR and SPT (+) to ragweed. Total n = 62, active group n = 30 (18m), placebo group n = 30 (10m). Aged from 21 to 61 yrs.
Interventions	Treatment: short ragweed extract. Pre-seasonal treatment given. Up-dosing phase included 2 groups according to sensitivity to ragweed in SPT: (a) severe sensitivity group received 10 injections (starting at 0.015 mcg AgE) and (b) mild sensitivity group received 6 injections (starting at 0.15 mcg AgE). Duration of treatment was 2 years.
Outcomes	Patient symptom/medication scores recorded in diary cards. Adverse events. Specific IgE and IgG antibodies.
Notes	2 sub-groups in year. Data from year 2 was not included for the analysis. The nurses administering the injections were aware of who was receiving active treatment or placebo, although they did not participate in the assessment of outcomes, which was done by another investigator who was blinded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Jutel 2005

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Poland and Germany. Inclusion criteria: SAR (+) moderate-severe to grass pollen that requires medication during the previous pollen season. SPT(+), RAST-CAP (+) > 2, and CPT (+). No SIT previous last 3 yrs. Total n = 57. Active n = 29 (21m). Placebo = 28 (16m)

Jutel 2005 *(Continued)*

	Median age: 25 yrs. Mild-moderate seasonal asthmatics were included.
Interventions	Treatment: a mixture of 5 recombinant grass pollen allergens. Median cumulative dose was 490 ug total protein, or 122.5 ug each of Phl p 1, Phl p 5a, and Phl p 5b, and 61.25 ug of Phl p 2 and Phl p 6. Median number of injections per participant in each group was 25. Duration: Jan 2002 until Sep 2003.
Outcomes	Symptom/medication scores recorded by patients during the pollen season. RQLQ. CPT. Adverse events. Specific IgE , IgG1, IgG4.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Karmaker 1994

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: India. Inclusion criteria: Clinical symptoms of rhinitis +/- asthma and SPT (+) to cocos nucifera tree pollen. Total n = 105, active n = 86, placebo n = 19. Aged 6 to 56 yrs.
Interventions	Treatment: cocos nucifera pollen extract. Total treatment duration and dosage given were not reported.
Outcomes	Patient symptom/medication scores. Adverse events. Serum specific IgE and IgG.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lee 1982

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: clinical symptoms of SAR +/- asthma and SPT (+) to mountain cedar pollen. Total n = 90, active group n = 48 (28m), placebo group n = 28 (17m). Age range 18 - 50 years.
Interventions	Treatment: mountain cedar allergenic extract. Mean number of injections 14.4-15.6 per subject. Mean starting dose: 6.99 PNU in SDET (serial dilution end point titration) group and 0.16 PNU in traditional IT group. Mean final dose: 245 PNU in SDET group and 82 PNU in traditional IT group.
Outcomes	Patient symptom/medication scores. Adverse events. Total serum IgE. Serum allergen specific IgE.
Notes	Study design included 3 study groups: traditional IT, SDET and placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Leynadier 2001

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: France. Inclusion criteria: SAR(+) +/- seasonal asthma, SPT(+), RAST (+) and nasal provocation test (+) to grass pollens (orchard, meadow, rye, sweet vernal and timothy). Total n = 29; active group n = 16 (7m), placebo group n = 13 (7m). Aged 18-44 years.
Interventions	Treatment: standardised 5-grass-pollen extract adsorbed onto calcium phosphate. 16 weekly injections were given as induction phase and maintenance was given monthly. Duration was 1 year.
Outcomes	Patient symptom/medication scores. Adverse events. Nasal provocation test. SPT responses. Serum IgE and IgG4 levels.

Leynadier 2001 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Litwin 1991

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: SAR(+), SPT (+) and RAST (+) to ragweed. Total n = 39; active group n = 20 and placebo n = 19. Aged 21 to 50 years. No sex distribution given.
Interventions	Treatment: Peptic fragment of a short ragweed pollen given weekly. Final dose achieved was approx 13 ug Amb a I.
Outcomes	Symptom/medication score recorded in diary cards. Adverse events. Antigen specific IgE and IgG .
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Meriney 1986

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: Clinical history of SAR, intradermal (2+) to ragweed pollen. Total n = 20 (9m), allergoid group n = 10, placebo group n = 10. Aged 21-52 yrs
Interventions	Treatment: allergoid ragweed extract. Duration of treatment was 20 weeks with 13 injections total. Max dosage 4000 PNU.
Outcomes	Patient symptom scores.

Meriney 1986 *(Continued)*

	Adverse events. Allergen specific-IgE and IgG. Total serum IgE. Pollen count.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Metzger 1981

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA and England. Inclusion criteria: clinical history of SAR and SPT(+) to ragweed pollen. Total n = 100; active group n = 50, placebo group n = 50. No sex or age distribution reported.
Interventions	Treatment: glutaraldehyde-modified, tyrosine-adsorbed ragweed extract. A total of 5 weekly pre-seasonal injections were given. Dosages 350, 1000, 3000, 6000 and 6000 PNU.
Outcomes	Patient symptom score. Adverse events. Overall evaluation. Antigen specific IgE and IgG. Pollen count.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Mirone 2004

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Italy. Inclusion criteria: SAR (+), SPT (+) and CAP (+) to Ambrosia.

Mirone 2004 *(Continued)*

	Total n = 32. Active n = 16 (7m). Placebo = 16 (11m). 13 patients had mild-moderate seasonal asthma (6 in active group). Age range: 23- 60 yrs.
Interventions	Treatment: Biologically standardised extract of Ambrosia artemisiifolia pollen absorbed onto aluminium hydroxide (ALK-Abello). 10, 100 and 1000 STU/ml (0.09, 0.9 and 9 ug/ml of the major allergen AMb a 1) were used. Duration: 1 year.
Outcomes	Symptom/medication scores recorded by patients during the pollen season. Skin challenge. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Norman 1982

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: clinical history of SAR or mild asthma and intradermal (+) to ragweed pollen. Total N = 20, active n = 10, placebo n = 10. Aged 18-55 yrs. No sex distribution given.
Interventions	Treatment: 1/20 w/v 50% glycerinated extract of short ragweed pollen. Ragweed allergoid and placebo given in clustered regimen, unaltered ragweed extract (allergen) given in a weekly regimen.
Outcomes	Patient symptom-medication scores using daily diaries. Adverse reactions. Specific IgE levels and IgG antibody levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ortolani 1984

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Italy and USA. Inclusion criteria: clinical history of rhinitis and asthma, SPT(+) and RAST(+) only to timothy grass pollen. Total n = 15; active group n = 8 (4m), placebo group n = 7 (2m). Aged 15-45 yrs.
Interventions	Treatment: Aqueous lyophized extract was purified and consisted of 33% velvet, 33% sweet vernal and 33% timothy grass pollen. The average single max dosage was 6000 RAST units and the mean cumulative dose was 18,700 RAST units.
Outcomes	Patient symptom/ medication score recorded by diary cards. Adverse events. Nasal secretions. Specific bronchial provocation test. Antigen specific IgE and IgG (total and subclasses 1 to 4). Pollen count.
Notes	10,000 RAST units = 7000 PNU

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ortolani 1994

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Italy. Inclusion criteria: SAR(+), SPT (+) and RAST(+) to Parietaria judaica. Total n = 35; active group n = 18(7m) and placebo n = 17(7m). Age range 14 to 59. Some patients with seasonal asthma.
Interventions	Treatment: aqueous extract of Parietaria judaica. Total 12 injections at weekly intervals with doses from 1 to 800 U.
Outcomes	Symptom/medication scores recorded by patients. Adverse reactions. Nasal, conjunctival and skin reactivity was assessed. Specific IgE, IgG1 and IgG4.

Ortolani 1994 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Paraskevopoulos 2005

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: UK. Inclusion criteria SAR (+) inadequately controlled with standard medication. SPT (+) and RAST (+) to Phleum pratense. No SIT previous 5 yrs. Total n = 18. Active group 100,000 SQ-U n = 12 (7m).
Interventions	Treatment: standardised depot preparations of grass pollen extract (Alutard SQ-U Phleum pratense, ALK-Abello) were given by subcutaneous injection. The up-dosing phase consisted of 15 injections over 8 weeks.
Outcomes	Late skin response.
Notes	Alutard Phleum pratense 100,000 SQ-U (ALK-Abello) corresponds to 20 µg of major allergen Phl p 5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Parker 1989

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: USA. Inclusion criteria: SAR (+) and SPT (+) to mountain cedar pollen. No SIT previous 5 years. Total n = 51. Active n = 26(13m). Placebo = 25 (12m). Age range: 22-75 yrs. No asthma data given.
Interventions	Treatment: Mountain cedar (Juniperus ashei) extract which contains 3.18 mg of protein per ml. Up-dosing schedule from 0.1 ml with increments of 0.05 to 0.1 ml until the highest dose of 0.5 ml was reached.
Outcomes	Symptom/medication scores recorded by patients during the pollen season. Adverse events. Immediate and late cutaneous response.

Parker 1989 *(Continued)*

	Serum sIgE, sIgG1 and sIgG4.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pastorello 1992

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Italy and Germany. Inclusion criteria: SAR(+), SPT (+) and RAST(+) to mixed grass pollen. Total n = 19; active group n = 10 and placebo group n = 9. m = 7. Age range 18 to 56. Some patients with seasonal asthma.
Interventions	Treatment: grass allergoid obtain by mild formalinisation of a grass pollen extract (six grasses, Dactylis glomerata, Festuca elatio, Holcus lanatus, Phleum pratense, Lolium perenne and Poa pratensis). Maximum concentration of 20,000 PNU.
Outcomes	Symptoms/medication scores recorded by patients. Adverse reactions. Nasal and skin reactivity. Specific IgE, IgG1 and IgG4.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Tari 1997

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Italy and Germany. Inclusion criteria: clinical history of rhinitis +/- asthma, SPT(+), RAST(+) and nasal provocation test (+) to Parietaria pollen. Total n = 40; allergoid group n = 20 (10m), placebo group n = 20 (10m). Aged 13-50 yrs.

Tari 1997 *(Continued)*

	Asthma n = 14 in allergoid group, n = 10 in placebo group.
Interventions	Treatment: Alum-adsorbed Parietaria pollen allergoid. Mean cumulative treatment dose in up-dosing phase was 1,500 TU and in maintenance phase was 24,500 TU.
Outcomes	Patient symptom/medication scores. Adverse events. Nasal and skin reactivity. Nasal inspiratory peak flow. Total and specific IgE and IgG.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Varney 1991

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: England. Inclusion criteria: severe SAR to timothy grass pollen with poor drug control +/- mild seasonal asthma. SPT (+) and RAST (+) to timothy grass pollen. Total n = 40, active group n = 21 (14m) and placebo group n = 19 (8m). Age range 19-52 years.
Interventions	Treatment: Purified and standardised extract of Pheum pratense Alutard SQ-aluminium adsorbed for slow release. Up-dosing phase: 8 weeks/15 injections; max dosage 30,000 BU. Maintenance dosage was 30,000 BU every 4 weeks.
Outcomes	Symptom/medication scores reported by patients in diary cards (May to September). Adverse events. Immediate and late skin responses and immediate conjunctival response to allergen challenge. Global assessment. Pollen counts.
Notes	1000,000 SQ/ml = 30,000 BU/ml Phleum pratense. During pollen season maintenance doses were reduced by 40% in all patients. The observation period was 2 hours after each injection.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Walker 2001

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: England. Inclusion criteria: severe SAR to timothy grass pollen with poor drug control +/- mild seasonal asthma. SPT (+) and RAST (+) to timothy grass pollen. Total n = 44, active group n = 22 (10m) and placebo group n = 22 (13m). Age range 22-64 years.
Interventions	Treatment: standardised, aluminium hydroxide-absorbed, depot Phleum pratense (timothy) grass pollen vaccine. Rapid up-dosing cluster regimen for 4 weeks, followed by monthly injections for 2 years. Maintenance dosage was 100,000 SQ units (20 mcg of allergen) every month. Patients were pre-treated with an antihistamine at least 15 minutes before each visit.
Outcomes	Symptom/medication scores reported by patients in diary cards (May to September). Adverse events. Health-related quality of life. Measurements of non-specific bronchial responsiveness. Local cutaneous reactions within 1 hour were recorded. Patients recorded any delayed (within 48 hours) local or generalised symptoms. Intradermal allergen challenges were performed with grass pollen extract; immediate (15 mins) and late (6 hrs) skin responses were recorded. Pollen counts.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Zenner 1997

Methods	Randomised, double-blind, placebo controlled trial.
Participants	Country: Germany. Inclusion criteria: clinical history of SAR to grass and/or rye pollen. SPT (+) to grass (Dactylis glomerata, Lolium perenne, Avena elatior, Phleum pratense, Poa pratensis, and Festuca pratensis) and rye, Secale cereale. Total n = 87; active group n = 45 (30m) and placebo n = 42 (29m). Age range 16 to 53.

Zenner 1997 *(Continued)*

Interventions	Treatment: tree pollen allergen extract of grass (Dactylis glomerata, Lolium perenne, Avena elatior, Phleum pratense, Poa pratensis, and Festuca pratensis) and rye (Secale cereale) for 7 weeks before the beginning of the grass-pollen season. Concentrations of 3, 10, 30, 100, 300, 600 and 1000 SE/ml.
Outcomes	Symptom/medication scores recorded by patients. Nasal, conjunctival and bronchial assessments. Adverse reactions. Specific IgE and IgG4.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ag = antigen
AU = allergy unit
AUeq = allergy units equivalent
BGP = Bermuda grass pollen
BPT = bronchial provocation test
BU = biologic unit
CPT = conjunctival provocation test
GOID = unfractionated allergoid
HMW-GOID = high-molecular-weight formalinised allergoid
Ig = immunoglobulin
IR = index of reactivity
IT = immunotherapy
IU = international unit
MPL = monophosphoryl lipid A
PNU = protein nitrogen unit
RAST = radioallergosorbent test
SAR = seasonal allergic rhinitis
SDET = serial dilution end point titration
SE = specific units
SIT = allergen-specific immunotherapy
SPT = skin prick test
SQ = standard quality
SQ-U = standard quality units
TE = therapeutische einheiten (therapeutic units)
TU = [not specified by author]
VAS = visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aabel 2000	Other route of immunotherapy (oral tablets).
Adelroth 1999	No standardised allergen extracts used.
Adelroth 2000	No standardised allergen extracts used.

Study	Reason for exclusion
Ancill 1990	Not a specific immunotherapy study.
Andre 2000	Other route of immunotherapy (sublingual tablets).
Astarita 1996	Single or low dose used (intradermal).
Bacal 1978	Not a double-blind study (single).
Barrett 2000	Not a specific immunotherapy study.
Berkovitz 2005	Not allergen extracts used.
Bernstein 1976	Some patients had previous immunotherapy.
Berstein 2001	Not a specific immunotherapy study.
Bochenska 2003	Not a specific immunotherapy study.
Bodtger 2003	Data included in another paper (Bodtger 2002).
Bolhaar 2004	Not a seasonal allergic rhinitis study (food allergy syndrome study).
Bonifazi 1991	Not a placebo controlled study.
Boznanski 1996	Not a double-blind placebo controlled study.
Brown 1964	Not a randomised controlled trial.
Bruce 1997	Patients were asthmatics, not rhinitics.
Brunet 1992b	Data included in another paper (Brunet 1992).
Bruno 1986	Not a double-blind randomised placebo controlled study.
Caffarelli 2000	Other route of immunotherapy (oral).
Calderon 2003	Data included in another paper (Frew 2006).
Cantani 1984	Not a placebo controlled study.
Caramia 1996	Not a double-blind placebo controlled study.
Charpin 1985	Not allergen extracts used.
Chyrek-Borowska 1995	Not a seasonal allergic rhinitis study (house dust mite allergy included).
Cirla 1996	Other route of immunotherapy (intranasal).
Cockcroft 1977	Low dose used (only 4 injections).
Connell 1967	Not a double-blind placebo controlled study.
Creticos 1996	Patients were asthmatics, not rhinitics.
Creticos 2003	Not a placebo controlled study.

Study	Reason for exclusion
Crimi 2001	Other outcomes investigated. Data included in another paper (Polosa 2003).
D'Amato 1996	Not a placebo controlled study.
Demoly 2002	Peptide immunotherapy used.
Di Stanislao 1997	Single injection of low dose used.
Dokic 1996	Not a double-blind placebo controlled study.
Donat 1981	Not a randomised study.
Donovan 1996	Not a placebo controlled study.
Dorward 1984	Not a placebo controlled study.
Durham 1991	A review article.
Durham 1996	Other outcomes investigated.
Durham 1999	Withdrawal of treatment study.
Durham 1999a	Other outcomes investigated.
Dykewicz 1998	Not a double-blind randomised placebo controlled study.
Egger 1997	Other outcome investigated.
Eng 2006	Follow-up study after immunotherapy discontinuation.
Eriksson 1979	Not a placebo controlled study.
Fal 2002	Not a placebo controlled study.
Fell 1990	Single injection used.
Fontana 1966	No standardised allergen extracts used.
Frankland 1954	Not a double-blind randomised placebo controlled study.
Frankland 1963	Not a double-blind randomised placebo controlled study.
Franklin 1967	Not a placebo controlled study.
Frostad 1980	Not a double-blind randomised placebo controlled study.
Frostad 1983	Not a placebo controlled study.
Furin 1991	Not a placebo controlled study.
Gabriel 1977	Not a seasonal allergic rhinitis study (perennial rhinitis study).
Galvain 1999	Review article.
Garcia Gonzalez 2002	Not a seasonal allergic rhinitis study (food allergy syndrome study).

Study	Reason for exclusion
Garcia-Selles 2003	Not a placebo controlled study.
Gehlhar 1998	Not a placebo controlled study.
Gietkiewicz 2001	Not a placebo controlled study.
Giovannini 2005	Not a placebo controlled study.
Girard 1988	Not a specific immunotherapy study.
Gonzalez 2002	Not a placebo controlled study.
Goor 1971	Not a double-blind randomised placebo controlled study.
Gordon 1972	Not a placebo controlled study.
Grammer 1985	Not a double-blind randomised placebo controlled study.
Guardia 2004	Not a placebo controlled study.
Haahtela 1984	Not a double-blind study (open).
Hauser 2003	Not a specific immunotherapy study.
Hayashi 1998	Other outcomes investigated.
Hendrix 1980	Not a placebo controlled study.
Hill 1982	Patients were asthmatics, not rhinitics.
Hofman 1997a	Not a placebo controlled study.
Hofman 1997b	Not a placebo controlled study.
Horak 1980	Not a double-blind randomised placebo controlled study.
Ipsen 1988	Not a double-blind randomised placebo controlled study.
Ito 1996	Not a double-blind placebo controlled study.
Johansson 1974	Not a placebo controlled study.
Juniper 1986	Not a double-blind placebo controlled study.
Kakinoki 2000	Not a placebo controlled study.
Karlsson 1986	Not a seasonal allergic rhinitis study (Cladosporium herbarum allergy study).
Kasatkin 1976	Not a specific immunotherapy study.
Kemker 1999	Survey study.
Kerr 1963	Not a randomised study.
Kerr 1964	Not a double-blind placebo controlled study.

Study	Reason for exclusion
Keskin 2004	Not a double-blind study (open).
Keskin 2005	Other outcomes investigated.
Kjellman 1980	Not a double-blind placebo controlled study.
Kleine-Tebbe 2005	Other route of immunotherapy (oral tablets).
Kleine-Tebbe 2006	Other route of immunotherapy (oral tablets).
Kleinjans 2004	Not a double-blind placebo controlled study.
Klimek 1999a	Not a placebo controlled study.
Klimek 1999b	Not a placebo controlled study.
Klimek 2005	Not a placebo controlled study.
Kuhn 1983	Not a placebo controlled study.
Kuhn 1985	Not a double-blind randomised placebo controlled study.
Lavigne 2002	Not allergen extracts used.
Leiferman 1975	Not a specific immunotherapy study.
Levy 1971	Not a double-blind randomised placebo controlled study and previous immunotherapy was given.
Li 1990	Not a specific immunotherapy study.
Lichtenstein 1968	Not a randomised controlled trial.
Lichtenstein 1971	Not a double-blind study.
Lichtenstein 1973	Not a double-blind study.
Lindsay-Miller 1971	Not a double-blind randomised placebo controlled study.
Lombardi 2001	Other route of immunotherapy (oral tablets).
Lowell 1965	Not a double-blind randomised placebo controlled study.
Machiels 1990	Not a specific immunotherapy study.
Malling 1999	Patients were asthmatics, not rhinitics.
Manger 1984	Not a double-blind randomised placebo controlled study.
Martin Munoz 1996	Patients were asthmatics, not rhinitics.
Mastruzzo 2002	Other outcome investigated.
McAllen 1969	Not a randomised study.
Mewes 1999	Not a placebo controlled study.

Study	Reason for exclusion
Miller 1974	Insufficient data available for analysis.
Miller 1976	Not a double-blind randomised placebo controlled study.
Mitchell 1971	Not a randomised study.
Moller 1989	Not a seasonal allergic rhinitis study (food hypersensitivity study).
Moller 2002	Not a double-blind placebo controlled study.
Mosbech 1987	Other route of immunotherapy (oral tablets).
Mosbech 1988	Other route of immunotherapy (oral tablets).
Moss 1987	Not a placebo controlled study.
Moverare 1998	Other outcomes investigated.
Moverare 2000	Not a placebo controlled study.
Muhlethaler 1990	Not a placebo controlled study.
Munoz Lejarazu 1993	Not a placebo controlled study.
Naclerio 1997	Withdrawal of treatment study.
Nakai 2002	Not a placebo controlled study.
Nakano 2002	Not a placebo controlled study.
Negro 1999	Not a double-blind placebo controlled study.
Nelson 1976	Not a placebo controlled study.
Niederberger 2004	Other outcomes investigated.
Nielsen 1996	Not a specific immunotherapy study.
Nolte 1999	Review article.
Norman 1968	Not a double-blind randomised placebo controlled study.
Norman 1969	Review article.
Norman 1971	Previous immunotherapy was given.
Norman 1972	Compares two different immunotherapy preparations.
Norman 1981	Not a double-blind randomised placebo controlled study. Long term efficacy study.
Norman 1984	Not a specific immunotherapy study.
Norman 1990b	Not a double-blind randomised placebo controlled study.
Nouri 2005	Other outcomes investigated.

Study	Reason for exclusion
Nouri-Aria 2004a	Other outcomes investigated.
Nouri-Aria 2004b	Other outcomes investigated.
Nowak-Wegrzyn 2004	Not a seasonal allergic rhinitis study (food allergy syndrome study).
Ohashi 1997	Not a specific immunotherapy study.
Olsen 1995	Not a placebo controlled study.
Osterballe 1980	Not a placebo controlled study.
Osterballe 1982	Not a placebo controlled study.
Osterballe 1982a	Not a placebo controlled study.
Osterballe 1982b	Not a placebo controlled study.
Osterballe 1982c	Not a placebo controlled study.
Osterballe 1982d	Not a placebo controlled study.
Osterballe 1982e	Not a placebo controlled study.
Osterballe 1983	Not a placebo controlled study.
Parr 1976	Not a specific immunotherapy study.
Pastorello 1987	Not a seasonal rhinitis study.
Pastorello 1988	Data included in another paper (Pastorello 1992).
Pence 1976	Some patients had previous immunotherapy.
Peng 1992	Not a placebo controlled study.
Pereira 2003	Not a specific immunotherapy study.
Petersen 1988	Not a placebo controlled study.
Pilette 2003	Other outcomes investigated.
Polosa 2003	Other outcomes investigated.
Pronk-Admiraal 2001	Other outcome investigated.
Radcliffe 1996	Not a seasonal allergic rhinitis study (perennial allergens).
Radcliffe 2003	Not a seasonal allergic rhinitis study (perennial allergens).
Rajakulasingam 1997	Not a specific immunotherapy study.
Rak 1988	Not a placebo controlled study.
Rak 1990	Not a double-blind placebo controlled study.

Study	Reason for exclusion
Rak 2001	Not a placebo controlled study.
Rasp 1999	Not a double-blind randomised placebo controlled study.
Ricca 1997	Not a placebo controlled study.
Roberts 2006	Immunotherapy in asthma.
Rogala 2004	Not a placebo controlled study.
Rover 2002	Other outcomes investigated.
Roznіecka 1995a	Other outcomes investigated.
Roznіecka 1995b	Not a double-blind randomised placebo controlled study.
Ruiz 2001	Not a double-blind placebo controlled study.
Sandstrom 2001	Not a specific immunotherapy study.
Scordamaglia 1992	Not a specific immunotherapy study.
Simon 1990a	Not a specific immunotherapy study.
Simon 1990b	Not a specific immunotherapy study.
Simons 2003	Other outcomes investigated.
Sin 1996	Not a seasonal allergic rhinitis study (perennials included).
Skoda-Turk 1980	Not a double-blind randomised placebo controlled study.
Sobel 1966	Not a double-blind placebo controlled study.
Soyogul 2005	Other outcomes investigated.
Spiegelman 1967	Not a double-blind placebo controlled study.
Stuck 2001	Other outcomes investigated.
Stuck 2004	Other outcomes investigated.
Sykora 2004	Not a double-blind study (single).
Symington 1977	Not a placebo controlled study.
Taudorf 1983	Other route of immunotherapy (oral tablets).
Te Pas 2004	Other route of immunotherapy (oral).
Troise 2000	Single dose used. Perennial allergens used.
Tulic 2004	Not allergen extracts used.
Turkeltaub 1990	Not a placebo controlled study.

Study	Reason for exclusion
Vaishnav 2005	Not whole allergen extract used.
Valovirta 1999	Not a placebo controlled study.
van Adelsberg 2003	Not a specific immunotherapy study.
Van Metre 1980a	Rinkel method used.
Van Metre 1980b	Rinkel method used.
van Metre 1982	Not a placebo controlled study.
Vanselow 1966	Not a specific immunotherapy study.
Varney 1992	Not a specific immunotherapy study.
Varney 1993	Other outcomes investigated.
Verstraeten 1987	Not a double-blind placebo controlled study.
Vittorio 1996	Not a placebo controlled study.
Wachholz 2002	Other outcomes investigated.
Wahn 2003	Not a specific immunotherapy study.
Walker 1995	Not a double-blind study (open and follow-up study).
Walker 2003	Withdrawal of treatment study.
Watanabe 2003	Other outcomes investigated.
Weyer 1981a	Two different immunotherapy preparations were used.
Weyer 1981b	Two different immunotherapy preparations were used.
Weyer 1990	Patients had previous immunotherapy.
Wihl 1988	Not a placebo controlled study.
Wilcock 2005	Other outcomes investigated.
Williams 2001	Other route of immunotherapy (nasal).
Williams 2002	Data included in another paper (Frank 2001).
Wilson 2001a	Other outcomes investigated.
Wilson 2001b	Other outcomes investigated.
Winther 2000a	Not a placebo controlled study.
Winther 2000b	Not a placebo controlled study.
Wuthrich 1968	Not a double-blind randomised placebo controlled study.

Study	Reason for exclusion
Wuthrich 1977	Not a double-blind randomised placebo controlled study.
Wuthrich 1980	Other outcomes investigated.
Yariktas 2002	Not a specific immunotherapy study.

Characteristics of ongoing studies *[ordered by study ID]*

Rajakulasingam 2006

Trial name or title	Study for evaluation of safety and efficacy of a pre-seasonal immunotherapy with an allergoid preparation of an extract of a 6 grass pollen mixture in patients with a clinically relevant grass pollen sensitivity.
Methods	
Participants	15-25 patients with rhinoconjunctivitis, otherwise healthy.
Interventions	[A] Allergoid preparation of 6 grass pollen mixture [B] Placebo sample group
Outcomes	Comparison of symptom and medication scores between treatment and placebo group. Changes in score of Rhinoconjunctivitis Quality of Life, documented by patient. Changes in patient assessed general well-being and allergic symptom visual anologue scales.
Starting date	1st January 2002
Contact information	K Rajakulasingam Department of Respiratory Medicine, Homerton University Hospital NHS Trust, Homerton Row, London, E9 6SR, UK. Tel: +44 20 8510 7030. Fax: +44 20 8510 7687
Notes	

DATA AND ANALYSES

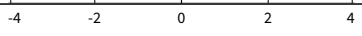
Comparison 1. Active versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom score	15	1063	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-0.97, -0.50]
2 Medication score	13	963	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.82, -0.33]
3 Symptom and medication	8	617	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.67, -0.29]
4 Nasal symptom	8	633	Std. Mean Difference (IV, Random, 95% CI)	-1.59 [-2.29, -0.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Bronchial symptom	5	429	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-1.06, -0.11]
6 Ocular symptom	3	345	Std. Mean Difference (IV, Random, 95% CI)	-1.80 [-3.28, -0.31]
7 IgG	4	191	Std. Mean Difference (IV, Random, 95% CI)	1.90 [0.88, 2.93]
8 IgG-4	5	404	Std. Mean Difference (IV, Random, 95% CI)	0.79 [0.49, 1.08]
9 Rhinoconjunctivitis Quality of Life score	5	571	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.69, -0.34]

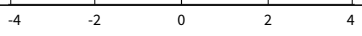
Analysis 1.1. Comparison 1 Active versus placebo, Outcome 1 Symptom score.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Balda 1998	49	6.6 (10.4)	56	9.1 (8.2)		9.33%	-0.27[-0.65,0.12]
Bodtger 2002	16	2.2 (1)	17	3.3 (1.4)		5.75%	-0.88[-1.6,-0.16]
Bousquet 1990	20	63.6 (32.5)	18	108.6 (33.2)		5.81%	-1.34[-2.05,-0.63]
Brewczynski 1999	10	59.5 (32.6)	8	122.4 (85.1)		3.84%	-0.98[-1.97,0.02]
Corrigan 2005	77	166.5 (114.9)	77	218 (135.4)		10.12%	-0.41[-0.73,-0.09]
Drachenberg 2001	74	0.8 (0.4)	50	1 (0.4)		9.59%	-0.46[-0.83,-0.1]
Ferrer 2005	22	0.4 (0.3)	20	0.8 (0.5)		6.55%	-0.81[-1.44,-0.17]
Frew 2006	187	3.3 (2.4)	89	4.6 (2.9)		10.85%	-0.49[-0.75,-0.24]
Jutel 2005	29	3.9 (3.3)	28	5.8 (3.4)		7.62%	-0.55[-1.08,-0.02]
Meriney 1986	10	3.5 (3)	10	8.4 (4.2)		3.91%	-1.29[-2.27,-0.3]
Ortolani 1984	8	2 (0.6)	7	5.9 (1.6)		1.78%	-3.06[-4.69,-1.43]
Ortolani 1994	18	0.6 (0.1)	17	2.3 (1)		4.45%	-2.4[-3.29,-1.51]
Varney 1991	19	1531 (1875)	16	2230 (856)		6.14%	-0.46[-1.13,0.22]
Walker 2001	17	-1212 (2632)	13	-115 (1159)		5.61%	-0.5[-1.24,0.23]
Zenner 1997	41	82.2 (64.4)	40	116 (83.7)		8.65%	-0.45[-0.89,-0.01]
Total ***	**597**		**466**			**100%**	**-0.73[-0.97,-0.5]**
Heterogeneity: Tau^2=0.12; Chi^2=38.05, df=14(P=0); I^2=63.21%							
Test for overall effect: Z=6.1(P<0.0001)							



Analysis 1.2. Comparison 1 Active versus placebo, Outcome 2 Medication score.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Balda 1998	49	9 (16)	56	13.6 (19.7)		10.47%	-0.25[-0.64,0.13]
Bodtger 2002	17	9.9 (7)	17	14.5 (8.5)		6.74%	-0.58[-1.26,0.11]
Bousquet 1990	20	38.6 (37.6)	18	66.4 (51.7)		7.1%	-0.61[-1.26,0.05]
Brewczynski 1999	10	17.2 (10.4)	8	36.8 (35.5)		4.45%	-0.76[-1.73,0.22]



Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Corrigan 2005	77	68.6 (96.2)	77	101.2 (126)		11.4%	-0.29[-0.61,0.03]
Dolz 1996	18	6 (6.1)	10	48.7 (18)		3%	-3.56[-4.82,-2.29]
Drachenberg 2001	74	0.5 (0.7)	50	0.7 (0.8)		10.82%	-0.23[-0.59,0.13]
Ferrer 2005	22	0.4 (0.5)	20	0.9 (1.7)		7.53%	-0.45[-1.06,0.16]
Frew 2006	187	2.9 (3)	89	4.3 (3.5)		12.21%	-0.43[-0.69,-0.18]
Jutel 2005	29	2.7 (4.5)	28	3.8 (4.9)		8.65%	-0.22[-0.74,0.3]
Mirone 2004	11	0.7 (1.4)	12	2.2 (3.1)		5.37%	-0.59[-1.43,0.25]
Varney 1991	19	2146 (2513)	16	14491 (15066)		6.36%	-1.17[-1.89,-0.44]
Walker 2001	16	-1308 (983)	13	101 (1899)		5.9%	-0.94[-1.71,-0.16]
Total ***	**549**		**414**			**100%**	**-0.57[-0.82,-0.33]**
Heterogeneity: Tau^2=0.11; Chi^2=33.35, df=12(P=0); I^2=64.02%							
Test for overall effect: Z=4.54(P<0.0001)							

Favours treatment -4 -2 0 2 4 Favours control

Analysis 1.3. Comparison 1 Active versus placebo, Outcome 3 Symptom and medication.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Balda 1998	49	201.4 (97.4)	56	221.3 (87.5)		17.18%	-0.21[-0.6,0.17]
Corrigan 2005	77	235.1 (172)	77	319.2 (201.7)		21.94%	-0.45[-0.77,-0.13]
Drachenberg 2001	74	0.7 (0.5)	50	0.8 (0.5)		18.68%	-0.38[-0.74,-0.01]
Ferrer 2005	22	0.6 (0.4)	20	1.3 (1)		7.77%	-0.84[-1.47,-0.21]
Jutel 2005	29	6.7 (6)	28	9.6 (7.2)		10.65%	-0.44[-0.96,0.09]
Ortolani 1994	18	12.9 (3.6)	17	17.8 (4.9)		6.23%	-1.12[-1.84,-0.4]
Pastorello 1992	10	1.7 (0.6)	9	3.2 (1.5)		3.39%	-1.22[-2.22,-0.22]
Zenner 1997	41	153.8 (63.5)	40	174.5 (59)		14.17%	-0.33[-0.77,0.1]
Total ***	**320**		**297**			**100%**	**-0.48[-0.67,-0.29]**
Heterogeneity: Tau^2=0.02; Chi^2=8.98, df=7(P=0.25); I^2=22.05%							
Test for overall effect: Z=4.9(P<0.0001)							

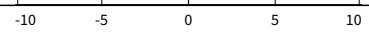
Favours treatment -4 -2 0 2 4 Favours control

Analysis 1.4. Comparison 1 Active versus placebo, Outcome 4 Nasal symptom.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Balda 1998	49	2.8 (4.3)	56	4.4 (4.4)		14.95%	-0.37[-0.76,0.02]
Bousquet 1987b	39	61 (17.9)	19	109 (16.8)		13.29%	-2.7[-3.45,-1.95]
D'Amato 1995	9	24.6 (18.4)	11	78.5 (5.6)		8.44%	-3.98[-5.62,-2.35]
Dolz 1996	18	0.1 (0.2)	10	1.4 (0.2)		6.82%	-6.59[-8.6,-4.57]
Ferrer 2005	22	0.6 (0.4)	20	0.9 (0.6)		13.93%	-0.68[-1.31,-0.06]
Frew 2006	187	2.1 (1.5)	89	2.9 (1.9)		15.34%	-0.53[-0.78,-0.27]
Mirone 2004	11	4 (3.3)	12	8.3 (4.2)		12.51%	-1.09[-1.98,-0.2]
Zenner 1997	41	44.5 (32.2)	40	63.3 (38.3)		14.74%	-0.53[-0.97,-0.08]

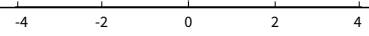
Favours treatment -10 -5 0 5 10 Favours control

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Total ***	**376**		**257**			**100%**	**-1.59[-2.29,-0.89]**
Heterogeneity: Tau^2=0.81; Chi^2=81.44, df=7(P<0.0001); I^2=91.4%							
Test for overall effect: Z=4.45(P<0.0001)							



Analysis 1.5. Comparison 1 Active versus placebo, Outcome 5 Bronchial symptom.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Balda 1998	29	0.7 (2.9)	32	3.2 (3.6)		22.11%	-0.75[-1.27,-0.23]
Dolz 1996	18	0.2 (0.2)	10	0.5 (0)		14.51%	-1.6[-2.49,-0.7]
Ferrer 2005	22	0.3 (0.3)	20	0.5 (0.7)		20.06%	-0.4[-1.01,0.21]
Frew 2006	186	0.5 (0.9)	89	0.6 (1.1)		27.8%	-0.08[-0.33,0.17]
Mirone 2004	11	0.4 (0.7)	12	0.9 (1)		15.53%	-0.55[-1.39,0.28]
Total ***	**266**		**163**			**100%**	**-0.59[-1.06,-0.11]**
Heterogeneity: Tau^2=0.19; Chi^2=14.21, df=4(P=0.01); I^2=71.85%							
Test for overall effect: Z=2.43(P=0.02)							

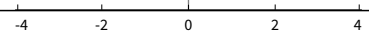


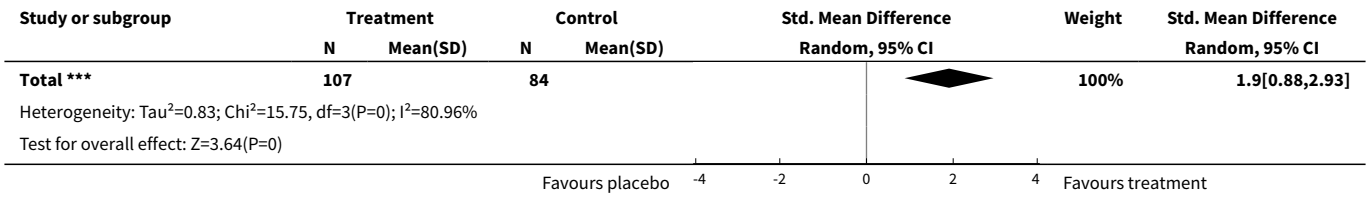
Analysis 1.6. Comparison 1 Active versus placebo, Outcome 6 Ocular symptom.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Dolz 1996	18	0.2 (0.2)	10	1.4 (0.2)		25.33%	-5.51[-7.25,-3.77]
Ferrer 2005	22	0.4 (0.5)	20	0.7 (0.7)		36.34%	-0.53[-1.14,0.09]
Frew 2006	186	0.9 (0.9)	89	1.4 (1)		38.33%	-0.55[-0.81,-0.3]
Total ***	**226**		**119**			**100%**	**-1.8[-3.28,-0.31]**
Heterogeneity: Tau^2=1.48; Chi^2=30.71, df=2(P<0.0001); I^2=93.49%							
Test for overall effect: Z=2.37(P=0.02)							

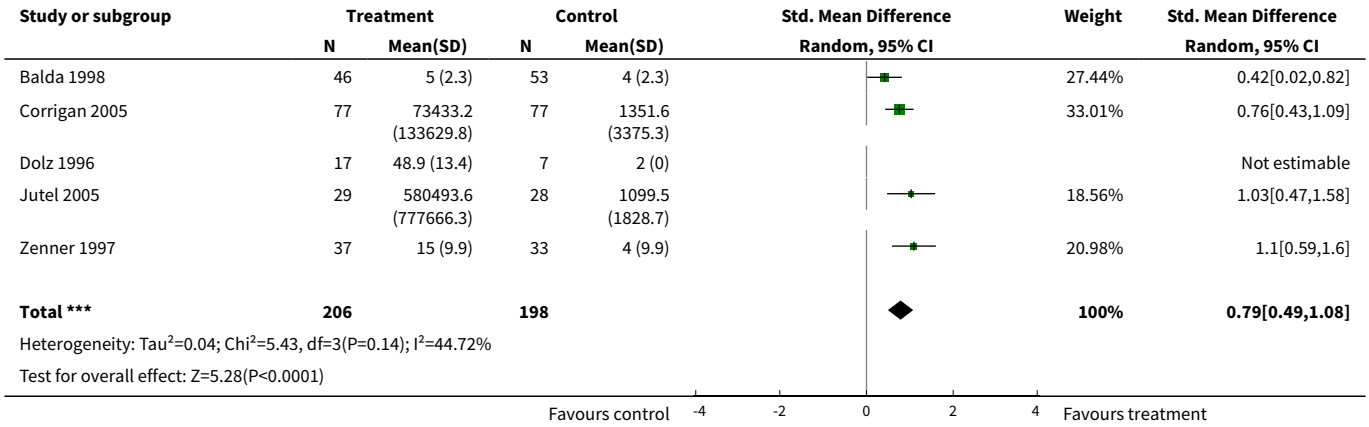
Analysis 1.7. Comparison 1 Active versus placebo, Outcome 7 IgG.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Drachenberg 2001	71	13.8 (11.3)	51	5.9 (3.5)		31.65%	0.88[0.5,1.26]
Ortolani 1984	8	15356 (3667)	7	3729 (3580)		18.18%	3.02[1.4,4.63]
Ortolani 1994	18	1758 (974.8)	17	52.4 (35.7)		26.5%	2.38[1.49,3.27]
Pastorello 1992	10	1239 (758)	9	142 (87)		23.67%	1.89[0.76,3.01]

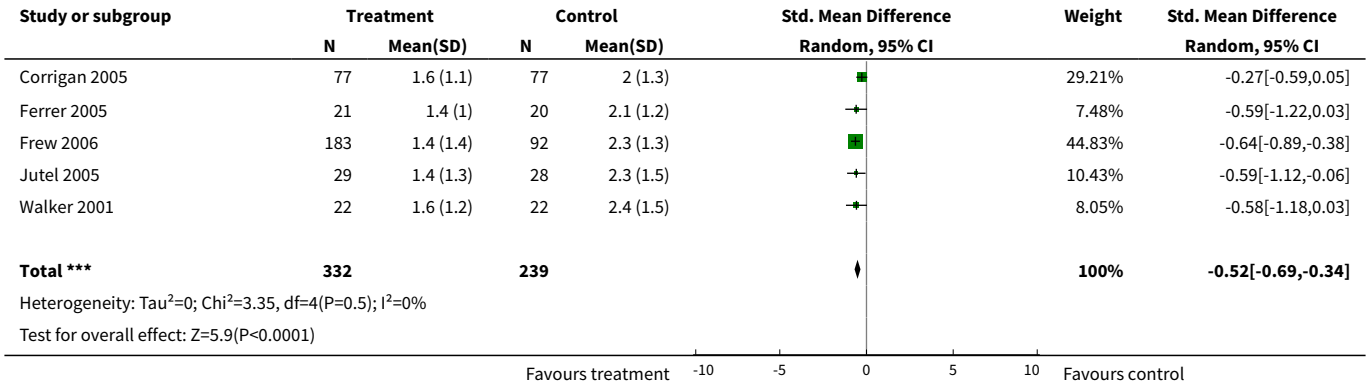




Analysis 1.8. Comparison 1 Active versus placebo, Outcome 8 IgG-4.



Analysis 1.9. Comparison 1 Active versus placebo, Outcome 9 Rhinoconjunctivitis Quality of Life score.



ADDITIONAL TABLES

Table 1. Symptom score results: studies not in meta-analysis

Study ID	Results
Alvarez-Cuesta 2005	A significant improvement in symptom scores (P < 0.0001) was observed in the immunotherapy treated group compared with the placebo group (median (first and third quartiles) 4.00 (3.52 to 4.45) and 5.85 (4.96 to 6.81), respectively).

Table 1. Symptom score results: studies not in meta-analysis *(Continued)*

Armentia-Medina 1989	Patients who received specific immunotherapy demonstrated greater clinical improvement than the control group (P < 0.001).
Arvidsson 2002	Median symptom scores in the specific immunotherapy and placebo groups during the first pollen season were 1.3 (range 0 to 5.2) and 2.1 (range 0.6 to 5.6), P = 0.05. During the second pollen season the median symptom scores were 2.6 (range 0 to 6.5) and 4.3 (range 2.4 to 9.1), P = 0.005.
Bousquet 1987b	Symptoms recorded during the peak of the pollen season were significantly reduced (P < 0.01) in the specific immunotherapy group (61 ± 35) compared to placebo group (109 ± 33).
Bousquet 1988	Symptom scores were significantly (P < 0.005) reduced in the group of patients treated with allergoids, the mean number of symptomatic days ranged from 12.1 ± 11.3 in the specific immunotherapy to 25.9±3.8 in the placebo group.
Brunet 1992a	During the ragweed pollen season, daily symptom scores were significantly lower in the specific immunotherapy group than in patients receiving placebo (4.7 ± 0.7 versus 7.5 ± 1.2; P < 0.05).
Ceuppens 2004	We were unable to obtain complete symptom score data from the authors of this study, which is available only in abstract form.
Charpin 2003	A non-significant improvement (17%) in rhinitis symptoms was found at the peak of the 2001 pollen season. However, there was a significantly greater improvement at the peak of the 2002 pollen season (49%, P < 0.01).
D'Amato 1995	Patients in the specific immunotherapy group indicated a mean decrease from 77.2 to 29.6 (62%) after year one and from 77.2 to 24.6 (68%) after year two in nasal blockage. These same patients indicated a mean improvement from 70.4 to 26.0 (63%) after year one and from 70.4 to 27.8 (61%) after year two in rhinorrhoea. They also indicate a mean decrease from 68.7 to 29.4 (57%) after year one and from 68.7 to 25.1 (64%) after year two in sneezing. All these improvements were significantly (P < 0.01) greater than those indicated by the placebo group.
Drachenberg 2002	The active group (n = 57) has a significant superiority during the pollen season (P = 0.028) compared to the placebo group (n = 27).
Grammer 1982	Symptom score indices of the specific immunotherapy group were significantly lower than those of the placebo control group (P = 0.024).
Hauser 1997	The clinical improvement in the active treatment group at the end of the season was greater that the comparatively small placebo effect in the control group, and the difference between the groups was statistically significant (P < 0.01).
Juniper 1985	In year one participants who received polyethylene glycol (PEG)-modified ragweed extract consistently recorded less severity and duration of all symptoms, although this was not significant. In year two the PEG-modified ragweed treated participants recorded significantly less overall symptom severity (P = 0.007) and duration (P = 0.047).
Leynadier 2001	The overall symptoms score (mean area under curve (AUC)) was not significantly different between the immunotherapy group and the placebo group during grass-pollen exposure (49.6 versus 56.0, respectively).
Metzger 1981	A mean seasonal symptom score was computed for each subject and the mean total seasonal scores showed a significant difference (P < 0.02) for the placebo and treated groups.
Mirone 2004	A significant (P < 0.008) improvement in symptom scores was observed in the immunotherapy treated group compared with the placebo group (median (interquartile range) 4.5 (3.6-9.1) and 9.3 (4.1-12.9), respectively).

Table 2. Medication score results: studies not in meta-analysis

Study ID	Results
Alvarez-Cuesta 2005	A significant improvement in medication scores (P < 0.0001) was observed in the immunotherapy treated group compared with the placebo group (median (first and third quartiles) 1.17 (1.10 to 1.32) and 1.67 (1.53 to 1.88), respectively).
Arvidsson 2002	The placebo group used significantly more rescue medication than the specific immunotherapy group during both seasons (P = 0.004 in 1997 and P = 0.004 in 1998).
Brunet 1992a	The types and amounts of symptomatic medication taken by patients of either groups were not statistically different (0.9 ± 0.2 versus 0.7 ± 0.2; P = 0.6), and most importantly, patients with lower symptom scores (specific immunotherapy group) actually took less medication.
Ceuppens 2004	We were unable to obtain complete medication score data from the authors of this study, which is available only in abstract form.
Charpin 2003	No statistical difference was observed between the two groups of patients for medication consumption which nevertheless remained limited.
D'Amato 1995	Most patients in the specific immunotherapy group were able to decrease their medication usage during the course of the study. It did not appear that increasing medication use contributed to the efficacy observed in the active treatment group.
Drachenberg 2002	The need for symptomatic medication was significantly less with the active group than with placebo (P = 0.019), the mean scores differed about fivefold.
Juniper 1985	In year one the group one subjects required less antihistamines, nasal spray and eye drops, but this only reached overall significance for the eye drops (P = 0.02). In group two no difference in medication use was observed between specific immunotherapy and placebo groups. In year two, although the use of medications was less, it only reached significance for nose spray (P = 0.014) and eye drops (P = 0.025) during week six of the pollen season.
Leynadier 2001	The total medication score (mean AUC) was significantly lower in the immunotherapy group than in the placebo group (11 versus 41, P < 0.01).
Metzger 1981	A statistically significant difference was found between the placebo and treated groups for daily drug usage.
Mirone 2004	A significant (P < 0.0008) improvement in medication scores was observed in the immunotherapy treated group compared with the placebo group (median (interquartile range) 0.6 (0 to 2.4) and 2.8 (0.3 to 4.4), respectively).
Zenner 1997	The use of symptomatic drugs depended significantly on the severity of symptoms (P < 0.001). Symptomatic drugs were used in the specific immunotherapy group for 26.6% of the 70 days (10 weeks) with strongest symptoms during the grass pollen season and for 33% of the days in the placebo group (P=0.296).

Table 3. Symptom & medication score results: studies not in meta-analysis

Study ID	Results
Ariano 1999	The specific immunotherapy group showed a significant improvement already in year 1 of treatment in comparison to the placebo group (P = 0.02). After switching to the active treatment the for-

Table 3. Symptom & medication score results: studies not in meta-analysis *(Continued)*

	mer placebo group also showed a significant improvement from baseline values and their symptoms scores approximated those of the specific immunotherapy group.
Bousquet 1987a	Arithmetic means of daily medication scores and symptom scores showed a significant reduction in symptoms and medication use in the two treated groups (mixed pollen allergoid and standardised orchard grass pollen extract ($P < 0.05$ to $P < 0.005$). Patients treated with the standardised orchard grass pollen extract had lesser symptoms and lower medication scores, but the difference did not reach significance.
Bousquet 1988	There was a significant correlation ($P < 0.03$) between the number of days with symptoms and the severity of symptoms or medication scores in the specific immunotherapy group.
Bousquet 1991	Patients in both treated groups had a lower mean symptom-medication score. Only patients placed in the grass pollen treated groups had a significant clinical improvement by comparison to placebo treatment ($P < 0.04$). Some polysensitised patients placed in the specific immunotherapy group were largely improved.
Fling 1989	There were no significant differences between the symptom/medication scores of the active treatment group and the placebo-treated group. The authors stated that the pollen count during the 1987 season was quite low.
Grammer 1983	The symptom score indices of the individually polymerised grass group were significantly lower than those of the placebo control group.
Grammer 1986	IPG-treated patients had statistically lower symptom/medication scores in all weeks during the defined season ($P < 0.05$). Also, the season total and season rhinitis symptom/medication scores of IPG-treated patients for the period of evaluation were significantly lower than those of the placebo treated patients ($P < 0.05$).
Grammer 1987	The scores of the PRW-treated patients were significantly lower than those of the placebo treated patients. In addition, the PRW treated patients had statistically lower rhinitis symptom/medication scores in all three weeks of the primary pollen season ($P = 0.005$) and in all five weeks of the secondary pollen season ($P = 0.02$). The P values for the median weekly total symptom/medication scores are similar except for the fifth week of the secondary season, which is not significant.
Iliopoulos 1991	Patients receiving immunotherapy treatment reported significantly ($P < 0.04$) less severe symptom/medication scores than the placebo treated group during the pollen season.
Karmaker 1994	Before immunotherapy, it was observed that patients in both specific immunotherapy and placebo-treated groups had a similar mean symptom/medication score, whereas, after treatment only the specific immunotherapy treated patients had a significant clinical improvement compared to placebo treatment ($P < 0.005$). NOTE: mean values not given for inclusion in meta-analysis.
Lee 1982	Symptom and medication scores showed no statistically significant difference between the serial dilution end point titration (SDET), conventional immunotherapy and placebo groups. They all reached peak scores in early January and the scores all fell in parallel fashion thereafter. After several weeks of treatment, there was a trend in which the placebo group had the highest symptom/medication scores, the SDET had the lowest and the conventional immunotherapy group was intermediate.
Leynadier 2001	The cumulative symptom/medication score was significantly lower in the immunotherapy group than in the placebo group (64.5 versus 102.3, $P < 0.05$).
Litwin 1991	There was a statistically significant difference ($P = 0.0001$) between both active treatment groups' scores for total symptoms and medication compared with the placebo group. This difference was even greater when comparisons were made at the peak of the pollen season ($P < 0.0001$).
Norman 1982	The arithmetic mean score was 8.8 for the placebo and 5.1 and 5.3 for the allergoid and allergen groups, respectively. The differences between either of the two groups and the placebo group were

Table 3. Symptom & medication score results: studies not in meta-analysis *(Continued)*

	significant (P < 0.01). There was, however, no significant difference between the scores of allergen and allergoid groups.
Parker 1989	Symptom/medication scores were significantly lower in the actively treated group versus the placebo treated group (57.0 versus 129.9, P = 0.0001). There were no significant differences in symptom/medication scores for subjects with single positive skin tests versus subjects with multiple positive skin tests (87.5 versus 94.4, P = 0.6648).
Tari 1997	Comparison of the active treatment and placebo groups during the first year of the study showed significant differences between the groups in their response to natural exposure to the allergen as reflected in symptom scores and use of medication. Both the morning and evening nasal inspiratory peak flow (NIPF) rates were significantly increased in the active treatment group after 12 and 24 months. There were no significant increases in the placebo group after 12 months, but after treatment during the second year of the study, this group also recorded a significant improvement. In both groups of patients, the nasal inspiratory peak flow measurements were lower in the morning than in the evening.

Table 4. Nasal symptom scores: studies not in meta-analysis

Study ID	Results
Bousquet 1989	Participants in the placebo-treated group had a significantly higher mean score for symptoms and medication use than participants placed in the high-molecular-weight formalinised allergoid (HMW-GOID) treatment group or standardised allergen treatment group. Patients of the unfractionated allergoid (GOID) treatment group had a significantly greater mean number of symptomatic days than patients placed in the other two treatment groups (HMW-GOID and standardised allergen).
Juniper 1985	In year one the severity and duration of nasal symptoms was significantly lower in the active treatment group in weeks three and five (P < 0.05) of the ragweed pollen season. In year two the PEG-modified ragweed treated subjects recorded significantly less overall nasal symptom severity (P = 0.03).
Leynadier 2001	Mean nasal symptoms were not significantly different between the two groups when tested as single endpoints.
Ortolani 1994	Actively treated patients had significantly lower nasal symptoms than placebo patients, the scores were significantly lower for running nose (P = 0.0087) and sneezing (P = 0.0488). Nasal blockage was also less frequent in the active group than in the placebo group, but the difference did not achieve statistical significance.
Pastorello 1992	Actively treated patients had significantly (P < 0.01) lower nasal symptoms than the placebo group.
Tari 1997	Both the morning and evening nasal inspiratory peak flow (NIPF; L/min) rates were significantly increased in the active-treatment after 12 and 24 months compared with placebo group.
Varney 1991	There was a significant reduction in total nasal symptoms (P = 0.02, 49 versus 143 (38 to 111)), blocked nose (P = 0.03, 12 versus 44 (3 to 42)), runny nose (P = 0.03, 11 versus 43 (5 to 43)) when Alutard SQ was compared with placebo. Note: data for individual symptoms were presented as median Alutard versus median placebo (95% CI for difference between medians).
Walker 2001	Comparison of 1998 with 1996 showed that the symptom scores (median differences) fell by 49% in the immunotherapy group and 15% in the placebo group (P = 0.01).

Table 5. Bronchial symptom scores: studies not in meta-analysis

Study ID	Results
Arvidsson 2002	No significant differences between the groups with respect to PEF values were found during any of the pollen seasons.
Bousquet 1989	Patients receiving either GOID, HMW-GOID or standardised allergen had significantly lower mean symptom or medication scores than patients in the placebo treated group. There was no significant difference between the three treated groups.
Bousquet 1990	Asthma symptom scores (mean ± SD) were significantly lower in the high dosage (17.4 ± 20.2, P > 0.01 < 0.005) and low dosage (12.8 ± 16.8; P < 0.001) specific immunotherapy treated groups than in the placebo group 54.8 ± 23.0).
Mirone 2004	A significant (P < 0.0014) improvement in bronchial scores was observed in the immunotherapy treated group compared with the placebo group (median (interquartile range) 0.4 (0 to 1.3) and 0.8 (0.1 to 1.9) respectively).
Ortolani 1984	Mean score values for symptoms most related to lower respiratory allergy (shortness of breath, wheezing and cough) were lower in the treated group than the placebo (P < 0.01).
Ortolani 1994	Lung symptoms were negligible in both groups and were not considered in the statistical analysis.
Pastorello 1992	Actively treated patients had significantly (P < 0.05) lower bronchial symptoms than the placebo group.
Varney 1991	Chest symptoms were reduced in the active group after immunotherapy treatment when compared with placebo groups, but these differences were of only borderline significance.
Walker 2001	Comparison of 1998 with 1996 showed that chest symptom scores (median differences) were reduced by 90% in the immunotherapy group compared with 11% in the placebo group (P < 0.05). After two years of treatment there was no seasonal decrease in methacholine PC20 in the immunotherapy-treated group, compared with a reduction of almost three doubling doses (32 to 4.5 mg/mL) in the placebo group (P = 0.04).
Zenner 1997	Median bronchial symptoms were not significantly different if tested as single endpoints, however, the largest reduction (52%) of mean symptom scores was observed for bronchial symptoms. Significance was obtained with simultaneous analyses of nasal and bronchial symptoms (P = 0.03).

Table 6. Ocular symptom scores: studies not in meta-analysis

Study ID	Results
Bousquet 1989	Patients receiving either GOID, HMW-GOID or standardised allergen had a significantly lower symptom scores than patients in the placebo treated group, but patients in the HMW-GOID group had very few symptomatic days.
Charpin 2003	A statistically significant improvement (48%; P < 0.03) in conjunctivitis symptom score was found at the peak of the 2001 pollen season. This significant improvement was even greater at the peak of the 2002 pollen season (63%; P < 0.01).
Dolz 1996	The conjunctival symptoms showed a statistically significant improvement (P < 0.001) during the three years of the study. Active group n = 18, mean 0.15 (SD 0.22) and placebo group n = 10, mean 1.36 (SD 0.20).
Juniper 1985	In year one the severity and duration of eye symptoms was significantly lower in the active-treatment group in week three and five (P < 0.05) of the ragweed pollen season. In year two the PEG-

Table 6. Ocular symptom scores: studies not in meta-analysis *(Continued)*

	modified ragweed treated subjects recorded significantly less overall eye symptom severity (P = 0.006).
Leynadier 2001	Mean conjunctival symptoms were not significantly different between the two groups when tested as single endpoints (mean scores (AUC) given but not SD values).
Ortolani 1994	No differences were detected for eye symptoms between active and placebo groups.
Pastorello 1992	Actively treated patients had significantly (P < 0.05) lower conjunctival symptoms than the placebo group.
Varney 1991	There was a significant reduction in total eye symptoms (P = 0.02, 37 versus 87 (10 to 82)) and streaming eyes (P = 0.02, 0 versus 5 (0 to 9)) when Alutard SQ was compared with placebo. Itching eyes were also reduced but these differences were of only borderline significance. Note: data were presented as median Alutard versus median placebo (95% CI for difference between medians).
Zenner 1997	Median conjunctival symptoms were not significantly different if tested as single endpoints. Significance was obtained with simultaneous analyses of nasal and conjunctival symptoms (P = 0.042).

Table 7. Global improvement

Study ID	Results
Ariano 1999	A self-assessment of the efficacy of specific immunotherapy was performed after one year via questionnaire (+31.6% in immunotherapy group versus -15% in placebo, P = 0.01). The actively treated patients reported a subjective improvement from year one and this improvement remained unchanged during the whole treatment period up to four years after the discontinuation of specific immunotherapy. The former placebo group improved after switching to active treatment and maintained this improvement up to four years after specific immunotherapy discontinuation.
Balda 1998	The general analysis of all patients with an evaluable diary (intention-to-treat group) showed a significantly lower (P = 0.041) median maximum increase of the overall symptom score during exposure to hazel/alder pollen, with 1.5 in the specific immunotherapy treated group (n = 46) and 6.0 in the placebo group (n = 51).
Bodtger 2002	A significant improvement in patients' global improvement was reported in the specific immunotherapy group nine months after specific immunotherapy started compared with the placebo group.
D'Amato 1995	Significantly (P < 0.01) more patients in the specific immunotherapy group assessed their rhinitis symptoms as being better or much better (eight of nine, 89%) compared with the placebo group (0 of 11, 0%).
Ferrer 2005	According to clinician's (77%) and patients' (72%) criteria, patients who received active treatment with immunotherapy had a significant clinical improvement (P < 0.03) in their allergic disease.
Metzger 1981	A statistically significant difference was found between the placebo and treated groups for global evaluation.
Pastorello 1992	Data obtained directly from the authors indicated that after one year of treatment with immunotherapy 8 out of 10 patients receiving active treatment had a global improvement compared with 2 out of 9 patients receiving placebo.
Varney 1991	Post-seasonal assessments of the Alutard SQ treated groups according to the physician's and patients' assessments were measured on a scale from -3 ("a lot worse") to +3 ("a lot better"). The median values were determined and active versus placebo were compared, the P value was < 0.001 for

Table 7. Global improvement *(Continued)*

	both the physician (95% CI for difference in medians 2,3) and patient assessment (95% CI for difference medians 1,2) in favour of Alutard SQ.
Zenner 1997	Data obtained directly from the authors indicated that after 25 weeks treatment with immunotherapy 26 out of 41 patients receiving active treatment had a global improvement compared with 20 out of 40 patients receiving placebo.

Table 8. Specific IgG

Study	Result
Armentia-Medina 1989	A significant increase ($P < 0.05$) in specific IgG levels was detected in treated patients compared to controls.
Bousquet 1987a	Patients who received the placebo had similar mean IgG levels before and after specific immunotherapy. By contrast, patients who were treated with either six-mixed grass pollen allergoid or with the standardised allergen extract had a significant increase in IgG.
Bousquet 1987b	Serum grass pollen IgG levels were significantly increased ($P < 0.01$) in the treated group (233 ± 154) compared to placebo group (103±12) but there was no significant correlation between their titer and NPT or symptom scores.
Bousquet 1988	Mean serum-specific IgG titer was significantly increased ($P < 0.01$) in the allergoid treated group, whereas it remained stable in the placebo treated group.
Bousquet 1989	Patients receiving either GOID, HMW-GOID or standardised allergen had significantly increased specific IgG levels (% binding) after specific immunotherapy ($P < 0.01$, $P < 0.005$ and $P < 0.005$ respectively). There were no mean serum changes in the placebo group.
Bousquet 1990	Mean serum-specific IgG level did not change after specific immunotherapy in the placebo treated group, whereas it was significantly ($P < 0.01$ and $P < 0.001$) increased in both treated groups.
Bousquet 1991	Mean serum specific IgG level did not change after specific immunotherapy in the placebo treated group, whereas it was significantly ($P < 0.02$ and $P < 0.04$) increased in both active treated groups. There was no significant correlation between nasal symptom/medication scores and IgG or IgE levels.
Brewcczynski 1999	There was an increased in total IgG levels after one year specific immunotherapy treatment in the treated group compared with placebo.
Brunet 1992	IgG levels were significantly higher in the group of treated patients as compared to levels in untreated patients ($P < 0.01$).
Ceuppens 2004	Incomplete data in abstract, no reply from authors.
Dolz 1996	The determination of specific IgG detected significant differences between the active group and the placebo group ($P < 0.001$). A significant increase in specific IgG was observed in the specific immunotherapy group at the end of the study compared to the initial time of the study. No changes were observed in the placebo group.
Drachenberg 2001	Blood levels of pollen-specific IgG antibody were raised significantly ($P = 0.01$ for all data points except baseline) by active treatment and another such rise was seen at the middle of the assessment period.

Table 8. Specific IgG *(Continued)*

Fling 1989	A significant difference was noted before the season and intraseasonally, with the specific immunotherapy group having greater amounts of specific IgG compared to the placebo group, P = 0.018 and 0.028, respectively.
Grammer 1982	Total serum antibody against AgE was measured. In the specific immunotherapy group there was a greater than 40-fold increase in blocking antibody, while there was no change in placebo treated patients.
Grammer 1983	A modest rise in IgE directed against rye grass group 1 (RGG1). However, after 48,000 PNU of individually polymerised grass, blocking antibody against RGG1 rose nine-fold, averaging 591 ng RGG1 bound/ml.
Grammer 1986	In the IPG-treated patients, there was a statistically significant eleven-fold increase in IgG to grass pollen (P < 0.0007) whereas there was no change in placebo treated patients.
Grammer 1987	The change in IgE against AgE in placebo and PRW treated patients showed a statistically significant 1.3-fold rise in PRW treated patients (P = 0.0024) but no change in placebo treated patients.
Hauser 1997	Increases in the grass-specific IgG were only detectable in the active treatment group. The median value immediately after therapy was 158% greater that the initial value, and at this point and the three time points during the pollen season, the allergen specific IgG level was significantly higher in the treatment group as compared with the placebo group (P = 0.0007, P = 0.0043, P = 0.0005, P = 0.0014, respectively). There were no significant changes in the placebo group.
Iliopoulos 1991	After the ragweed season, the difference between immunotherapy treated and placebo treated groups was statistically significant (2445 versus 500 ng/ml; P < 0.001) for specific IgG levels.
Juniper 1985	Injections of PEG-modified ragweed also stimulated increases in IgG; when the increases were compared with placebo treated group levels, the increase reached significance both in year 1 (both groups P = 0.032) and also in year 2 (P = 0.008). Both years the increases in IgG were linearly related to the total dose of PEG-modified ragweed injected (P < 0.0001).
Karmakar 1994	After immunotherapy specific IgG levels were statistically significant higher (P < 0.025) in the specific immunotherapy treated group (mean SD; 582 26) compared to placebo group (mean SD; 469 37).
Litwin 1991	After immunotherapy treatment, the mean increase of specific IgG was 106.4% in Pool 2-treated patients and 59.1% in fSRW-treated patients (P < 0.05). The difference between the two groups was not statistically significant. Specific IgG increased 1% in placebo treated patients. However, there was a fall in specific IgG levels during seasonal exposure for both active treated groups, -10.1% in the fSRW-group and -3.2% in the Pool 2-treated patients. The decreased seasonal specific IgG found in each of these two groups was statistically significant when compared with the placebo treated patients (P < 0.05) but not when compared with each other.
Meriney 1986	In the treatment group, post-treatment blocking antibodies levels showed a consistent and significant rise compared with pre-treatment levels (P = 0.001). No significant rise in blocking antibody levels after therapy was observed in the control group. Absolute levels of post-treatment blocking antibody were significantly higher in the treatment group when compared to the control group (P = 0.01), although there was no such difference prior to therapy. Post-season blocking antibody levels remained significantly elevated in the treatment group compared with the control group (P = 0.02).
Metzger 1981	The mean rise of antigen specific IgG was about six-fold, from 232 EU to 1276 EU of antibody activity (P < 0.001).
Norman 1982	The allergoid regimen produced a more rapid serum IgG antibody response, with significantly higher post-treatment levels than those in the allergen regimen.

Table 8. Specific IgG *(Continued)*

Ortolani 1984	Specific IgG antibody showed significant increases in treated subjects on comparison with controls after 4 months of immunotherapy (P < 0.005) that started from very low levels before institution of immunotherapy.
Ortolani 1994	There was an increase in specific IgG associated with active treatment. The levels peaked at the third assessment (after 5 months of immunotherapy) and then stayed fairly level. No changes were observed in the placebo group.
Pastorello 1992	The actively treated group showed a statistically significant increase (P < 0.0005) in mean IgG level after 2 months of immunotherapy (855 PNU). The maximum mean level was reached after 4 months (46,050 PNU). At subsequent determinations, after 9 and 12 months of immunotherapy, the level was somewhat below the maximum but the increase was still significant (P < 0.001) after 9 months and after 12 months (P < 0.02). No changes were observed in the placebo group.
Tari 1997	After 6 months treatment, the IgG antibody levels were significantly increased (P < 0.01) in the active group, and levels remained significantly greater than the baseline values at later time points in the study. No changes were detected in the placebo group.

Table 9. Specific IgG4

Study	Result
Ariano 1999	A significant increase was observed in the active group (but not in the placebo one) after 1 year of treatment, and this effect remained unchanged at years 2 and 3 (P < 0.01). After switching to active treatment, the previously placebo group also shown an increased in serum IgG4.
Balda 1998	Specific IgG4 significantly increased (P < 0.001) in SIT group but remained unchanged in the placebo group at T1 (after therapy). IgG4 continued to increase slightly in the SIT group at T2 (in season) and decreased at T3 (after season). IgG4 only slightly increased at T2 and T3 in the placebo group.
Brewcczynski 1999	There was an increase in specific IgG4 levels after one year specific immunotherapy treatment in the treated group compared with placebo.
Dolz 1996	For specific IgG4, an important increase was seen in the active group in comparison with the control group, in which there was no change (P < 0.001). The increase of IgG4 was later than that of specific IgG, although it reached high and progressive values.
Fling 1989	No significant differences for specific IgG4 levels were present between the treated patients and those receiving placebo before specific immunotherapy, but levels were significantly higher in the specific immunotherapy treated group before the season and intraseasonally.
Jutel 2005	IgG4 concentrations showed a continuing upward trend, achieving an approximately 4000-fold increase by the end of treatment. Comparisons between the groups showed statistically significant differences at all time points after the commencement of immunotherapy (P < 0.001).
Leynadier 2001	Mean serum specific IgG4 levels in the immunotherapy group increased more than fivefold (from 3.2% to 17%, P < 0.001) during the pollen season, then decreased slightly after the season (from 17% to 10.7%). In the placebo group, specific IgG4 levels remained unchanged during and after the pollen season.
Ortolani 1984	Significant increases were observed in each of the four IgG subclasses with a statistically greater increase of IgG4 (P < 0.05) relative to baseline when compared with IgG antibodies 1 to 3. After achieving maintenance dose around the fifth month of therapy, a decrease in IgG antibodies of all subclasses was observed. This decrease was significant for total IgG class antibodies in October

Table 9. Specific IgG4 *(Continued)*

	as compared to April 1981 (P < 0.05). Nevertheless, differences in IgG and IgG antibodies 1 to 4 between treated subjects and controls remained highly significant at the end of the trial.
Ortolani 1994	In the active group, P.j.-specific IgG1 peaked after 5 months of immunotherapy and then declined; P.j.-specific IgG4 antibodies reached their peak levels at the same assessment, but remained high. No changes in specific IgG1 and IgG4 levels were detected in the placebo group.
Parker 1989	Both MC sIgG1 and MC sIgG4 levels were significantly higher in actively treated subjects than in control subjects, P < 0.001. Both MC sIgG1 and MC sIgG4 levels rose in the placebo treated subjects, presumably because of natural exposure to MC pollen, P = 0.0479 and P = 0.0024, respectively.
Pastorello 1992	Specific Ig4 showed a significant increase (P < 0.05) after 2 months of immunotherapy, followed by a constant increase, reaching the maximum mean level after 4 months. This level remained constant until after 12 months. No changes were observed in the placebo group.
Tari 1997	Specific IgG1 levels were significantly increased after 6 months of active treatment (P < 0.01), but decline thereafter as the treatment continued. Increases in specific IgG4 were not seen until 12 months after commencement of therapy, and levels remained significantly raised during the second year of treatment. There were no significant changes in IgG1 and IgG4 in the placebo group.
Zenner 1997	Specific IgG4 levels with specific immunotherapy were increased at T1 by more than 400% (P < 0.001) and continued at this level up to T3. Patients treated with the maximum dose of 1000 SE had higher levels of IgG4 at T1, T2 and T3 compared to patients who received lower doses.

Table 10. Specific IgE

Study	Result
Ariano 1999	After 1 year of immunotherapy, a significant increase in specific IgE was observed only in the actively treated group (P = 0.004). Subsequently, the IgE concentration constantly and significantly decreased (baseline versus year 2: P = 0.04; baseline versus year 3: P = 0.003). No change was detectable in the placebo group after year 1. After year 2 of immunotherapy there was a significant fall in IgE levels (baseline versus year 2: P = 0.01; baseline versus year 3: P = 0.006), this was also observed in the placebo group.
Armentia-Medina 1989	A significant increased (P < 0.001) in specific IgE in the treated patients compared to the control group.
Balda 1998	The course of specific IgE in the specific immunotherapy and placebo groups showed only slight, insignificant differences from higher mean values after placebo. The adjusted mean curves were (T0-T1-T2-T3) 61,56-67.36-1.74-68.85 SU/ml in the specific immunotherapy group and 61.56-69.41-72.02-75.11 SU/ml in the placebo group.
Bodtger 2002	Neither the birch pollen specific IgE nor the total IgE differed significantly between the groups at any measurement. Both parameters increased in both groups but only the increase in total IgE levels in the placebo group reached significance.
Bousquet 1987a	Grass pollen IgE was very similar before and after specific immunotherapy in the placebo treated group and was non-significantly increased in the other two treated groups.
Bousquet 1988	Mean serum IgE was significantly (P < 0.04) increased in the allergoid treated patients (23.7 ± 11.6% before treatment to 31.4 ± 13.5% after treatment) and remained stable in the placebo treated group.

Table 10. Specific IgE *(Continued)*

Bousquet 1989	There was an increase in mean levels of specific IgE (% binding) in patients receiving either GOID, HMW-GOID or standardised allergen, but this was only significant in the HMW-GOID treated group (P < 0.01). There were no mean serum changes in the placebo group.
Bousquet 1990	After specific immunotherapy, mean serum-specific IgE levels increased non-significantly in the two allergoid treated groups, and there was no change in the placebo treated group.
Brewcczynski 1999	No changes were observed in specific IgE levels after one year specific immunotherapy treatment in the treated group and the placebo group.
Brunet 1992	The significant raise of IgE in the placebo treated group observed during the ragweed pollen season, as compared to preseasonal level 22551 ± 3779 versus 26159 ± 4222 counts per minute; P < 0.02) was prevented by specific immunotherapy (23196 ± 3985 versus 24938 ± 3952 counts per minute; P = NS.
Ceuppens 2004	Incomplete abstract, no reply from authors.
Corrigan 2005	The median serum concentration of allergen specific IgE declined during the two treatment periods in both groups and over the study as a whole. Mean values (SD) were 2.32 (2.96) for the active group compared with 3.44 (6.09) in the placebo group.
Dolz 1996	No significant changes were observed between the beginning and the end of the study for total IgE and specific IgE levels for both, the active and the placebo groups.
Drachenberg 2001	The active treatment group did not increase levels of grass pollen specific IgE antibody. In the placebo group, at the middle of the assessment period, a rise was found which was not seen in the active group (P = 0.002). Slight falls were observed in both groups after the end of the pollen season.
Fling 1989	There was a non-significant reduction of specific IgE levels measured during the pollen season in the specific immunotherapy compared to placebo.
Grammer 1986	There was no statistically significant rise in IgE against grass pollen in IPG- or placebo-treated patients. Statistical analyses were performed with log transformations of the data.
Grammer 1987	In the PRW-treated patients, there was a statistically significant nine-fold rise in total antibody binding of AgE (P < 0.00001), whereas there was no change in patients treated with placebo.
Iliopoulos 1991	The placebo treated group had a significant increase in IgE antibodies, 1.2 versus 1.73 median log, ng/ml, related to the season (P < 0.001). No increase occurred in the immunotherapy treated group (1.82 versus 1.71 median log, ng/ml, before and after season, respectively).
Juniper 1985	Both years injections of PEG-modified ragweed stimulated an increase in IgE, but when the changes were compared with the changes in the placebo-treated group, this only reached significance in group 1 the first year (P = 0.014).
Jutel 2005	Specific IgE levels were not significantly different between groups at the beginning of the study, but thereafter, those of the active treatment group were significantly less than placebo. Concentrations showed a downward trend, with values significantly less than baseline.
Karmakar 1994	After immunotherapy specific IgE levels were statistically significant higher (P < 0.001) in the placebo treated group (mean, SD; 783, 51) compared to specific immunotherapy group (mean, SD; 291, 32).
Lee 1982	The placebo and the traditional immunotherapy group showed a significant increase in serum IgE specific for mountain cedar antigen levels from pre-treatment to the season peak (P = 0.01). Increases in the SDET group were in the same periods. In both treatment groups, the decline of specific IgE levels from their peaks to the postseason period was significant (P = 0.01).

Table 10. Specific IgE *(Continued)*

Leynadier 2001	Before treatment, mean serum specific IgE levels were higher in the immunotherapy group than in the placebo group, but this difference was not statistically significant. During and after the pollen season, mean serum specific IgE levels remained unchanged in both the immunotherapy group and the placebo group.
Litwin 1991	A small increase in specific IgE occurred in both treatment groups prior to the ragweed season (+14.2% in the Pool 2 group and +3.9% in the fSRW group). A small decline in specific IgE (-9%) occurred among the placebo group. Comparison between groups was not significant. However, during seasonal exposure to ragweed, the placebo treated patients showed a mean rise in specific IgE of +89% and both allergen treatment groups abolished this expected increase. fSRW-treated patients showed the most profound effect with a mean increase in specific IgE of only +9.9%, this difference was significant ($P < 0.01$) when compared to placebo. Pool 2 treated patients also experienced a diminished anamnestic response of specific IgE as compared with placebo treated subjects with a mean increase of +14.7%, this was difference significant compared with controls ($P < 0.01$). Although fSRW treatment seemed to produce more suppressive effect than Pool 2 treatment, the difference between the two groups was not significant.
Meriney 1986	Specific IgE levels to ragweed was measured just after completion of immunotherapy (mid-August) and again after the ragweed season. Considerable variability was found in specific IgE levels but no significant differences between groups were observed.
Metzger 1981	There was an increase in the mean post-treatment antigen-specific IgE antibody activity from 17 to 27 EU ($P < 0.001$).
Norman 1982	The allergoid regimen produced a more rapid serum IgE antibody response, with significantly higher post-treatment levels than those in the allergen regimen.
Ortolani 1984	IgE antibody to timothy did not show significant variations either in the serum or in the secretions of treated subjects with respect to controls. No important seasonal variations were noted.
Ortolani 1994	No significant changes in IgE antibody level specific to P.j. pollen in undiluted and 1:5 diluted sera were detected in either actively or placebo treated patients during the entire trial.
Parker 1989	Post-seasonal levels of MC sIgE were significantly lower in actively treated subjects than in control subjects, $P = 0.0001$.
Pastorello 1992	As compared with baseline, the actively treated group presented a significant increase in specific IgE mean level after 3 ($P < 0.01$) and 4 ($P < 0.01$) months of immunotherapy. After 9 and 12 months of immunotherapy this group showed a decrease in specific IgE mean levels, reaching a value not different from baseline. The placebo group showed no noteworthy changes in specific IgE mean levels throughout the year.
Tari 1997	Specific IgE levels in the active treatment group did not change significantly during the course of the study, although there was a progressive trend to a lower concentration. There was an increase in the placebo group, but this was not statistically significant.
Zenner 1997	Levels of specific IgE adjusted to T0 significantly increased at T1 ($P = 0.006$) for specific immunotherapy treated patients but remained unchanged for placebo. Specific IgE levels showed a parallel increase for both groups at T2. Levels continued to increase in the placebo group, but decreased slightly in the specific immunotherapy group at T3.

Table 11. Nasal Challenge

Study	Result

Table 11. Nasal Challenge *(Continued)*

Bodtger 2002	No significant changes were observed after one year follow up (year 2000) in NPT (SQ-U) in the immunotherapy group versus placebo (P > 0.7).
Bousquet 1987b	Nasal challenges performed before the pollen season showed that the mean provocative dose is significantly increased (P < 0.01) in the treated group (28,036 ± 57,435) compared to placebo group (860 ± 1394).
Bousquet 1988	After specific immunotherapy with allergoids, the mean number of grains eliciting nasal symptoms ranged from 217 ± 150 grains to 14,723± grains (P < 0.005). In contrast, patients who received placebo only had a slight and non-significant improvement in the provocative dose (430 ± 505 grains to 1360 ± 3793 grains).
Bousquet 1990	After specific immunotherapy the mean number of grains eliciting nasal symptoms ranged from 21,932 ± 51,104 grains (P <0.04) in the low dose group or from 33,530 ± 63,003 grains (P < 0.01) in the high dose group. There were no significant differences between the two groups. The correlation between the threshold dose inducing nasal challenge and the observed symptoms of the patients during the season was highly significant (P < 0.001). Most patients with a positive NPT for a low number of pollen grains (50 to 250 grains) suffered from severe symptoms during the pollen season. In contrast, most patients who reacted during the NPT for a high number of pollen grains (>6250 grains) had fewer symptoms during the pollen season.
Bousquet 1991	Patients in the grass pollen treated group reacted for a significantly (P < 0.01) greater mean number of grains (m ± SD; 69,175 ± 70,655 grains) than patients in the corresponding placebo treated group (44-fold increment). In contrast, patients in the multiple pollen treated group reacted for a non-significantly greater mean number of grains (m ± SD; 28,687 ± 51,437 grains) by comparison to the corresponding placebo treatment (9.3-fold increment). There was no significant difference between active treated groups.
Brunet 1992	The ragweed specific nasal reactivity measured during the pollen season was significantly higher in the placebo treated group than in the actively treated group. More ragweed extracts were needed to induce a drop of NAR in ragweed treated patients than in placebo treated subjects, especially at PD50 (614 ± 114 versus 118 ± 98 PNU; P < 0.002) and PD75 (901 ± 113 versus 163 ± 114 PNU; P < 0.0001). Furthermore, natural exposure to pollen did not significantly affect the nasal reactivity to ragweed in ragweed treated patients (P = 0.44).
D'Amato 1995	After 2 years of treatment significantly more (P < 0.01) specific immunotherapy patients (seven of nine, 78%) indicated improvement, relative to baseline, than did placebo patients (one of eleven, 9%).
Iliopoulos 1991	Immunotherapy significantly decreased the early reaction to nasal challenge with antigen. The levels of histamine, TAME-esterase activity and kinins, as well as the symptoms generated during the early reaction of the immunotherapy treated group, were significantly lower than the corresponding levels of the placebo treated group (P < 0.02 for all). Four to 10 hours after ER, the levels of TAME-esterase activity, kinins and symptoms generated in the entire immunotherapy-treated group were lower than the corresponding levels of the entire placebo treated group, but these difference did not reach statistical significance. Levels of histamine in the late phase reaction were the same in both groups. The levels of histamine, TAME-esterase activity, kinins and symptoms generated during the rechallenge reaction of the immunotherapy treated group were lower than the corresponding levels of the placebo treated group, but only the differences in symptoms reached statistical significance (P < 0.02).
Leynadier 2001	A threefold higher concentration of allergen extract (63.4 IR) was necessary in the immunotherapy group to elicit a positive response on NPT after immunotherapy (P < 0.05), but no such change was observed in the placebo group (31 IR before immunotherapy versus 37.7 after immunotherapy, P > 0.05). After immunotherapy, the threshold dose in the immunotherapy group was higher than in the placebo group (63.4 IR versus 37.7 IT, respectively), but these differences were not statistically significant.

Table 11. Nasal Challenge *(Continued)*

Ortolani 1994	The responses to NPT in the two groups showed that only the active group presented a significant increase in the nasal threshold dose of P.J. extract after 4 and 10 months of immunotherapy (P < 0.01). No correlations were found between symptom/medication scores and NPT.
Pastorello 1992	A significant decrease (P < 0.05) in specific nasal reactivity was detected in actively treated patients after 12 months of immunotherapy. No differences were found between the two groups after 4 months of immunotherapy. After 12 months of immunotherapy three patients no longer react to the top concentration (10,000 BU/ml). No differences were observed in the placebo group.
Tari 1997	Nasal provocation showed that there was no difference in sensitivity between the two patient groups at the beginning of the trial. After 12 months, there was a significant increase in the allergen provocation dose for the active treatment group from a median value of 600-2000 BU (P < 0.01), while there was a substantially smaller yet significant difference for the placebo group (P < 0.01). The difference between the groups was also significant (P < 0.01). After the second year of treatment, the provocation dose was increased still further to 5000 BU in the active-treatment group (P < 0.01).

Table 12. Conjunctival Challenge

Study	Result
Arvidsson 2002	No statistically significant differences between the active and placebo groups were seen in the conjunctival provocation test results.
Bodtger 2002	Conjunctival provocation test (SQ-U) in the specific immunotherapy groups was only significant as a paired analysis (P < 0.05) and not between the treatment groups, the median value did not change whereas the range did.
Corrigan 2005	A comparison of the two treatment groups at the end of the grass pollen season in 2003 showed a significant difference (P < 0.0001) in the concentration of allergen tolerated. 72% of patients in the active group improved their allergen tolerance.
Dolz 1996	The concentration of antigen necessary to make the conjunctival provocation test positive increased by 250 BU/ml in the active group (P < 0.001) between T0 and T4. No changes were seen in the placebo group.
Jutel 2005	All subjects fulfilled the inclusion criterion of a positive conjunctival provocation test. At the end of the study, there was a clear trend to a higher threshold allergen dose, although this was not statistically significant (P = 0.081).
Ortolani 1994	A significant increase of the conjunctival threshold dose of P.j extracts (alpha fractions) was found in conjunctival provocation tests after 4 months of immunotherapy (P < 0.05), whereas in the placebo group no changes were found. No correlations were found between symptom/medication scores and conjunctival provocation tests.
Varney 1991	Provocation tests showed a greater than 10-fold reduction for the active group in immediate conjunctival allergen sensitivity (P = 0.001) after immunotherapy treatment.

Table 13. Skin Challenge

Study	Result

Table 13. Skin Challenge *(Continued)*

Ariano 1999	A decrease in skin reactivity was observed in both groups at year 3 of treatment from baseline for the three allergen concentrations used (3 kAU/ml: 17.1 versus 14.2 mm, P = 0.02; 10 kAU/ml: 22.8 versus 19.2 mm, P = 0.01; 30 kAu/ml 27.2 versus 22.6 mm, P = 0.002).
Armentia-Medina 1989	A significant decrease (P < 0.001) in skin sensitivity to grass pollen was found in treated patients compared to controls.
Bodtger 2002	Specific immunotherapy reduced cutaneous late-phase response diameters (P < 0.00001).
Bousquet 1987a	The evolution of skin tests after specific immunotherapy demonstrated that patients treated with placebo did not present any significant change in their end point titer, whereas patients treated either with allergoid or the standardised orchard grass pollen extract had a significant (P < 0.01 and P < 0.02) decreased in their skin test end point.
Bousquet 1988	In the allergoid treated group, there was a significant (P < 0.001) decrease in skin test end point, whereas there was no major difference in the placebo-treated patients.
Bousquet 1989	Patients receiving either GOID, HMW-GOID or standardised allergen had a significant reduction in the mean end point titer for skin test reactivity to allergen (P < 0.04, P < 0.005 and P < 0.01 respectively) after specific immunotherapy. There were no mean changes in the placebo group.
Bousquet 1990	After specific immunotherapy, the mean end point titer of patients treated with placebo did not change by comparison to pretreatment and was significantly greater than end point of both treated groups (P < 0.05 and P < 0.02).
Bousquet 1991	There was only a significant (P < 0.01) difference between skin tests performed before and after specific immunotherapy in patients treated by grass pollen.
D'Amato 1995	The mean size of skin test reactions after 2 years of treatment was statistically significant (P < 0.01). The mean reaction had decreased 7.2, 18.4, 20.1 and 28.8 mm, relative to baseline, at the 8, 40, 200 and 1000 AUR/ml concentrations, respectively. Each of these decreases was significantly (P < 0.01) greater than those observed at the same concentrations in the placebo group.
Dolz 1996	The quantitative evaluation of the SPT from the onset to the end of the study showed a statistically significant decrease (P < 0.01) for the active group in comparison to the placebo group, which showed no significant variation. The concentration of antigen necessary to make the SPT positive increased in the active group (P < 0.001) between T0 and T4. No changes in the placebo group.
Drachenberg 2001	There were changes in skin test activity recorded before and after therapy. Activity was significantly reduced in the active group compared with placebo group for both the threshold values (P = 0.03) and the total wheal areas (P = 0.04).
Fling 1989	The 14 paired patients were matched according to the size of the late cutaneous reaction (LCR) to an intradermal injection of 0.02 ml of 1:1000 dilution of pollen extract. There was no significant difference in the size of the LCR before treatment in the two groups. However, there was a significant difference in the size of the LCR between the active therapy group and the group receiving placebo injection, P < 0.025. When the percent change in the LCR from baseline to intraseason was compared, the difference became more apparent with a P < 0.0005. Interestingly, there was a significant decrease not only in the specific immunotherapy group (P = 0.018) but also in the placebo group (P = 0.043). There was a significant difference in the size of the immediate cutaneous reaction (ICR) between the 7 matched patient pairs before specific immunotherapy with larger ICR in the placebo treated group (P < 0.005). However, there was no significant difference in the size of the ICR between both groups at the end of the study. Also, the percent change in the ICR from baseline was similar for both groups.
Iliopoulos 1991	The 15-minute wheal generated in the immunotherapy treated group was significantly smaller than the corresponding wheal in the placebo treated group (11.25 versus 14.25, median diameter in mm; P < 0.002). There was no significant difference in the 15-minute erythema formation (45.5 versus 52.25, median diameter in mm) during the early reaction. The effect of immunotherapy on

Table 13. Skin Challenge *(Continued)*

	the cutaneous late phase reaction (LPR) was more pronounced. Not only was the overall cutaneous LPR of the immunotherapy treated group smaller than the cutaneous LPR of the placebo treated group (43.5 versus 303.75, median diameter in mm; P < 0.002), but the immunotherapy-treated group also developed an erythematous induration (flare) that was significantly (P < 0.002) smaller than the corresponding induration of the placebo treated group for every hourly measurement.
Leynadier 2001	A significant difference (P < 0.001) was observed for each allergen concentration tested between the skin tests performed before and after immunotherapy in patients treated by grass pollens. In contrast, no significant change in skin test responses was observed in the placebo group. For the 100 IR/ml concentration, the mean wheal diameter decreased from 9.6 mm before immunotherapy to 6.7 mm after immunotherapy in the immunotherapy group versus slight increase from 9 mm to 9.3 mm in the placebo group. Comparison of the two groups showed a highly significant increase in allergic skin threshold for the immunotherapy group (P = 0.001).
Mirone 2004	The active group showed a significant decrease in the skin reactivity after treatment (13.44-fold in reference to baseline, P < 0.0001). In contrast, a slight increase by 1.07-fold (P = 0.87) was observed in the placebo group.
Ortolani 1994	There was a significant increase in the cutaneous threshold dose in the active group after 4 (P < 0.05) and 10 months (P < 0.01) of immunotherapy. No changes were observed in the placebo group. No correlations were found between symptom/medication scores and SPT.
Paraskevopoulos 2005	At the end of the up-dosing phase (approximately 8 weeks) there was a significant reduction in the size of the late phase response which was evident with all three intradermal doses (P = 0.02 for 0.1 and 1 BU, and P = 0.04 for 10 BU). This reduction was sustained throughout the maintenance phase (P = 0.04 for 0.1 BU, and P = 0.01 for 1 and 10 BU).
Parker 1989	Immunotherapy resulted in no significant change in the immediate cutaneous response. However, the late cutaneous response was significantly reduced; actively treated mean versus placebo treated mean was 8.59 cm versus 33.37 cm, respectively; P = 0.0001.
Pastorello 1992	A significant decrease (P < 0.02) in specific skin reactivity to the grass pollen extract was observed in actively treated patients after 4 and 12 months of immunotherapy; no differences were detected in the placebo group. No skin reactivity to histamine was detected in either group.
Tari 1997	Active treatment was associated with a significant reduction in the allergen/histamine wheal ratio, reflecting reduced skin sensitivity. During the course of the first year of treatment, the ratio decreased from a median value of 3.05 to 1.8 (P < 0.01); and by the end of the second year, the ratio was further reduced to 1.0 (P < 0.01). In the placebo group there was no change during the first year, but at the end of the second year, after 1 year of therapy, the ratio was decreased significantly to 1.75 (P < 0.01).
Varney 1991	After immunotherapy there was a significant (P = 0.02) reduction of 40% in the immediate (15 minutes) skin reaction in the Alutard treated group (median difference -7.5 mm) compared with the placebo group (median difference -3.5 mm). A significant (P < 0.001) reduction of 57% was also found in the late (24 hours) skin response in the Alutard treated group (median difference -36.5 mm) compared with the placebo group (median difference +14.9 mm).
Walker 2001	Both early (P = 0.007) and particularly late (P = 0.000) skin responses after intradermal allergen were markedly reduced after immunotherapy compared with placebo.
Zenner 1997	The threshold dose in skin prick test titration was higher in the actively treated group than in the placebo group at T1. This was not significant (P = 0.09) for the total number of patients but was significant (P = 0.005) for patient who reached the maximum dose of 1000 SE during the injection phase.

Table 14. Bronchial Challenge

Study	Result
Armentia-Medina 1989	A significant decrease in specific (P < 0.001) and non-specific (P < 0.05) BHR to grass pollen was found in treated patients compared to controls.
Dolz 1996	Bronchial provocation test comparison of initial time (T0) and end time (T4), showed an increase of 1000 UB which was necessary to make the active group positive (P < 0.001). There were no significant differences in the placebo group.
Ortolani 1984	The threshold of specific bronchial reactivity to provocation test PD 20% FeV1 did not show any variations either in patients who were treated with placebo or in those who received active antigen.

WHAT'S NEW

Date	Event	Description
25 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 1, 2007

Date	Event	Description
14 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

MOISES CALDERON: Lead author, searching for trials, quality assessment of trials, design of data extraction form, data extraction, data analysis, input at all other stages of review.

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MIKILA JACOBSON: Contribution to data analysis.

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AZIZ SHEIKH: Conceiving the review, leading protocol development, searching for trials, input at all other stages of review and supervision of review process.

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DECLARATIONS OF INTEREST

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INDEX TERMS

Medical Subject Headings (MeSH)

Allergens [*administration & dosage]; Desensitization, Immunologic [adverse effects] [*methods]; Injections, Subcutaneous; Pollen [adverse effects] [immunology]; Randomized Controlled Trials as Topic; Rhinitis, Allergic, Seasonal [*therapy]

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Humans