

REVIEW ARTICLE

Systematic reviews of sublingual immunotherapy (SLIT)S. Radulovic¹, D. Wilson², M. Calderon³ & S. Durham³¹Paediatric Allergy, King's College, London; ²Selly Oak Hospital, University Hospitals Birmingham NHS Trust, Birmingham, UK; ³Royal Brompton Hospital, Upper Respiratory Medicine, London, UK**To cite this article:** Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011; DOI: 10.1111/j.1398-9995.2011.02583.x.**Keywords**

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Abstract

Allergic rhinitis is common worldwide, with significant morbidity and impact on quality of life. In patients who don't respond adequately to anti-allergic drugs. Subcutaneous allergen immunotherapy is effective although requires specialist administration. Sublingual immunotherapy may represent an effective and safer alternative. This Cochrane systematic review is an update of one published in 2003. We searched Cochrane ENT Group Trials Register, Central, PubMed, EMBASE, CINAHL, Web of Science, Biosis Previews, Cambridge Scientific Abstracts, mRCT and additional sources. We included randomised, double-blind, placebo-controlled trials of sublingual immunotherapy in adults and children. Two authors selected studies and assessed them for quality. Data were put into RevMan 5.0 for a statistical analysis. We used standardised mean difference (SMD), with a random effect model to combine data. Sixty studies were included, with 49 suitable for meta-analysis. We found significant reductions in symptoms (SMD -0.49; 95%CI (-0.64 to -0.34, $P < 0.00001$)) and medication requirements (SMD -0.32; 95%CI (-0.43 to -0.21, $P < 0.00001$)) compared with placebo. None of the trials reported severe systemic reactions, anaphylaxis or use of Adrenaline. This updated review reinforces the conclusion of the original 2003 Cochrane Review that sublingual immunotherapy is effective for allergic rhinitis and appears a safe route of administration.

As evidenced by the publication of this special edition of the Journal, allergen-specific immunotherapy has been in clinical use for a century. For patients with severe allergic rhinitis who do not respond to usual therapy, specific immunotherapy, given by injection, induces immunomodulation resulting in significant reductions in symptoms and medication requirements (1) that continue beyond the cessation of treatment (2)

Although highly effective, allergen injection immunotherapy has significant drawbacks – local adverse events such as injection site itch or swelling are fairly common and, although rare, systemic reactions can be severe or even life-threatening. For this reason, the use of injection IT has been restricted to specialist centres and requires significant resources for its delivery.

In an attempt to eliminate these difficulties, alternative routes for the delivery of immunotherapy, ideally with equivalent efficacy and a better safety profile, have been sought. Over the last three decades, much attention has been focused on the sublingual route. Initial studies utilizing this route were small but suggested a favourable efficacy and safety profile leading to the design of bigger trials that continued

this trend but were individually insufficiently powered to give definitive answers.

The systematic reviews

In 2002, we undertook a systematic review of the literature in sublingual immunotherapy (SLIT) up to September 2002, using the methodology of the Cochrane Collaboration. Twenty-two randomized, placebo-controlled trials of adequate quality, involving 979 patients, were identified. The findings of this review and its meta-analysis were published in the Cochrane library (3) and subsequently in *Allergy* (4).

Despite significant heterogeneity between the trials, most likely due to widely differing scoring systems, the meta-analysis showed a significant reduction in both symptoms [standardized mean difference (SMD) -0.42, 95% confidence interval -0.69 to -0.15; $P = 0.002$] and medication requirements [SMD -0.43 (-0.63, -0.23); $P = 0.00003$] following immunotherapy. Subgroup analyses failed to identify any difference according to the allergen administered, and there was no significant reduction in symptoms and medication

scores in those studies involving only children. Adverse events reported in these trials were minor and local, and no systemic reactions were reported.

Subsequent to this review many further studies, of increasing size and quality, were published. In anticipation of producing an even more comprehensive evaluation of the efficacy and safety of SLIT and of answering some of the outstanding questions from the original review it was decided to repeat the systematic review and meta-analysis, updating it to 2009. The updated review is published in full in the Cochrane library and an abridged version is reproduced below (5).

Objectives

To evaluate the efficacy of SLIT compared with placebo in the following:

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

To evaluate the safety of SLIT.

Methods

Criteria for considering studies for this review

Types of studies

Randomized, double-blind, placebo-controlled clinical trials.

Types of participants

The studies included participants of any age (children and adults). All patients had a history of allergic rhinitis, with or without allergic conjunctivitis and with or without allergic asthma. In all studies, the allergen was clearly identified. Patients' sensitivity was proven by positive skin-prick tests and/or high specific IgE to a particular allergen. The existence of other clinically relevant sensitivities was one of the exclusion criteria in the majority of studies.

Trials dealing with asthma only were excluded from this review.

Types of interventions

Included studies were those investigating the efficacy and safety of SLIT. Trials were analysed regardless of treatment dose, duration or whether the allergen was swallowed or spat out.

Types of outcome measures

Primary outcomes. Symptom scores, however, recorded (either daily or weekly, via symptom score diaries, visual analogue scales, number of well days or overall assessment).

Medication scores referring to the use of relevant anti-allergic medications, however, recorded and scored.

Secondary outcomes. Measurement of serum IgE and IgG (total and specific), assessment of allergen sensitivity (eye, nose or skin), quality of life and adverse event reports.

Search methods for identification of studies

Systematic searches for randomized controlled trials were conducted. There were no language, publication year or publication status restrictions. The date of the last search was 14 August 2009. Full details of the search strategy can be found in the Cochrane Library version of the review (5).

Data collection and analysis

Selection of studies

Two authors (SR and MC) independently screened the search results and selected studies that appeared to meet the review inclusion, and all such studies were obtained in full text for further assessment. Any disagreements about which studies to include in the review were resolved by further discussion with the other two authors (SRD and DW).

Data extraction and management

Data were extracted from the included studies onto a standard form, covering study type and methodology, number and description of participants, details of type, dosage, schedule, duration of SLIT used, as well as the results, types, timing and method of outcome measures. One author (SR) extracted all data, and values were checked by MC and SRD. If published manuscripts did not report data in format suitable for meta-analysis, or if data were insufficient, further information was sought directly from the authors.

As all the review authors were previously familiar with the content of most of the studies, we did not remove the study author names before assessment and data extraction.

Assessment of risk of bias in included studies

For the original 2003 review, quality assessment of the trials was performed. Concealment of allocation and blinding of study participants and investigators was assessed according to the guidelines of The Cochrane Collaboration (6). For the 2010 update, all the originally included studies were scored using the Jadad scale (7) and then reassessed for risk of bias using the Cochrane Collaboration 'Risk of bias' tool as guided by *The Cochrane Handbook for Systematic Reviews of Intervention* (8).

Data synthesis

Apart from adverse events, all the outcome data analysed were continuous. The most common way of recording data was through daily diary cards, recording and scoring symptoms (nasal, eye or less frequently chest) and medication use (antihistamine tablets, nasal sprays, eye drops). These data were subsequently totalled and averaged.

A wide range of different scoring systems and scales were employed by trial authors for both, primary and secondary outcomes. This creates problems of heterogeneity but is unavoidable. Data were entered into RevMan 5 for statistical analysis (9) using the SMD (the difference in means between two treatment groups, immunotherapy and placebo, in units of pooled standard deviation).

Random-effect models were used for statistical analysis of the overall efficacy of SLIT, and the results are presented as SMDs with 95% confidence intervals (CI).

Heterogeneity between studies was analysed using the chi-squared test, with a P -value of <0.1 , indicating significant heterogeneity between studies. In addition, to further assess heterogeneity, we used the I^2 , statistic variable that describes the percentage of total variation across trials that is because of heterogeneity rather than sampling error. Threshold values recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (8) were used (0% to 40%: might not be important; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity).

Subgroup analysis was carried out according to the review protocol as follows:

- 1 seasonal vs perennial allergens;
- 2 children vs adults;
- 3 dosage of major allergen ($<5\text{ }\mu\text{g}$ of major allergen protein vs $5\text{--}20\text{ }\mu\text{g}$ vs $>20\text{ }\mu\text{g}$;
- 4 duration of immunotherapy (<6 months vs $6\text{--}12$ months vs >12 months, to cover preseasonal, perennial and prolonged treatment);
- 5 sublingual spit vs sublingual swallow
- 6 sublingual drops vs tablets.

Adverse events were analysed as discontinuous data, and only a descriptive analysis is presented.

Results

Results of the search

Description of studies

The updated searches in 2009 identified 628 papers of potential interest. A total of 498 papers were discarded after reading the abstracts (review articles or descriptive studies, papers investigating other routes of immunotherapy or not investigating allergic rhinitis). Hundred and thirty papers were therefore evaluated in detail. Following this evaluation, we discarded another 68 papers (Fig. 1).

Included studies

We thus identified 62 papers as potentially appropriate for the review and meta-analysis. We identified two studies as ongoing (Ingels 2002; O'Hehir 2005).

A total of 60 studies (10–71) are now included in the 2010 update of this review, of which 49 studies are included in the updated meta-analyses (Fig. 1). Eleven studies that did not contain efficacy data eligible for meta-analysis contained useful adverse event data.

Most trials were performed with grass pollen (23 studies). Other allergens used were *Parietaria* (five trials), ragweed (two trials), trees (nine trials: two olive, three cypress, two birch pollen, two mixed trees), house dust mite (eight trials) and cat (one trial). One of the trials investigated the efficacy of grass and birch pollen immunotherapy.

Thirty-four studies were performed in adults and 15 investigated efficacy and safety in children. Treatment lasted for

<6 months in 17 studies; $6\text{--}12$ months in 16 studies and longer than 12 months in 16 studies.

Of the 49 studies, 32 reported the major allergen dose in a manner suitable for meta-analysis. The rest of the trials either did not provide the sufficient data or reported the cumulative dose (weekly, monthly or a total cumulative dose over the complete treatment). Eight trials used daily doses of $<5\text{ }\mu\text{g}$, in 12 studies the dose was between 5 and $20\text{ }\mu\text{g}$ per day, and 12 papers reported a daily dose of more than $20\text{ }\mu\text{g}$.

Nine trials reported data on skin sensitivity, but only six (skin prick test after treatment) could be included in the meta-analysis. Seven trials reported data eligible for meta-analysis of nasal reactivity. Data on conjunctival reactivity were not sufficient for meta-analysis.

Excluded studies

A total of 24 studies are excluded from this review – these are detailed under 'characteristics of excluded studies' in the full review.

Risk of bias in included studies

All included studies were double-blind, placebo-controlled trials of parallel-group design. Concealment of treatment allocation was considered adequate in all studies, based on statements made by the original authors.

Blinding of study subjects and investigators was almost universally maintained by the use of identical placebo preparations. It should, however, be noted that most investigators reported high levels of minor oral side-effects (tingling, itching and swelling beneath the tongue) in actively treated subjects, which could influence blinding.

Full risk of bias assessments can be found in the characteristics of included studies' table and Figs 2 and 3 of the full review.

Effects of interventions

Symptom scores

A total of 2333 active treatment (SLIT) and 2256 placebo patients were included. The combined SMD following SLIT was -0.49 (95% CI -0.64 to -0.34) favouring active treatment ($P < 0.00001$). There was significant heterogeneity between the studies ($\chi^2 = 256.76$, $P < 0.00001$, $I^2 = 81\%$) (Fig. 2)

Medication scores

Thirty-eight trials reported medication score results, with a total of 1737 patients in the SLIT group and 1642 in the placebo group. The combined SMD was -0.32 (95% CI -0.43 to -0.21 , $P < 0.00001$). Significant heterogeneity was indicated ($\chi^2 = 73.32$, $P = 0.0003$, $I^2 = 50\%$) (Fig. 3).

Data from subgroup analyses for symptom and medication scores are summarized in Tables 1 and 2.

Specific serum antibodies

Fourteen studies reported increases in serum-specific IgE levels in a manner suitable for the meta-analysis, with 675 participants in the SLIT and 659 in the placebo group. The

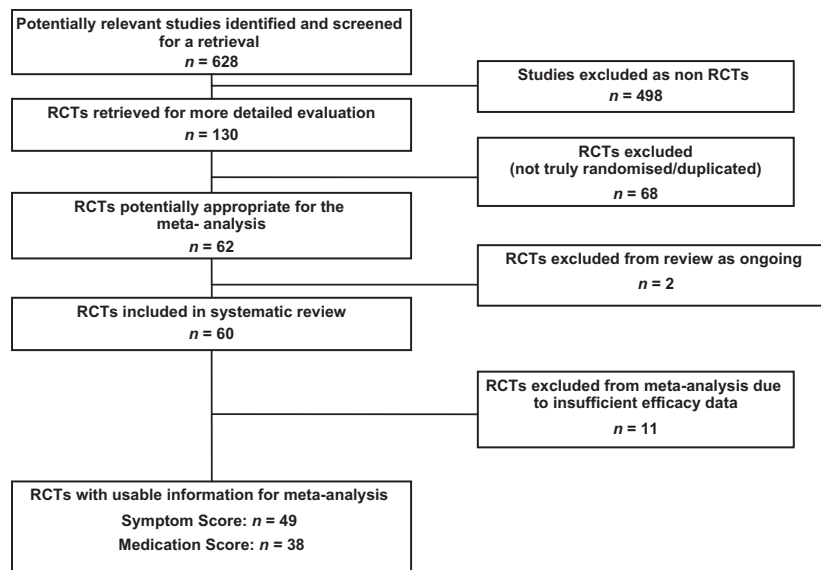


Figure 1 Consort chart.

combined SMD was 0.27 (95% CI -0.01 to 0.55 , $P = 0.05$). Significant heterogeneity was indicated between studies ($\chi^2 = 68.63$, $P < 0.00001$, $I^2 = 81\%$).

Total serum-specific IgG was measured in three studies, with 286 participants in the SLIT and 304 in the placebo group. The combined SMD was 0.95 (95% CI 0.78 to 1.12 , $P < 0.00001$). There was no significant heterogeneity between studies ($\chi^2 = 1.01$, $P = 0.60$, $I^2 = 0\%$).

Serum-specific IgG4 was measured in 13 trials, with a total number of 588 in the SLIT and 599 in the placebo group. The total SMD was 0.46 (95% CI 0.29 to 0.63 , $P < 0.00001$). Highly significant heterogeneity was indicated ($\chi^2 = 174.24$, $P < 0.00001$, $I^2 = 93\%$).

Adverse events

All sixty studies in the review were analysed for safety results.

Not all studies included data on adverse events. The lack of a standardized grading system for reporting of adverse events associated with SLIT required that events be presented as descriptive data only. Of the 60 studies evaluated for safety, twenty-five studies reported different local events and systemic reactions were reported by 18 studies (Table 3). Local adverse events were more common in immunotherapy-treated patients, whereas the majority of reported adverse events were mild to moderate and did not require any treatment. Fifteen studies reported adverse events leading to withdrawal from studies. In the SLIT group, 41 of 824 (5%) withdrew because of adverse events compared to 12 out of 861 (1%) of placebo-treated participants. Systemic adverse events were common in both placebo- and SLIT-treated participants and of mild-to-moderate intensity. There were no apparent differences between sublingual and placebo-treated participants (Table 3), with the exception of gastro-

intestinal symptoms that were more common in the sublingual group (88 of 630 participants, 14%) compared to placebo-treated participants (10 of 561, 1.7%). It is debatable whether gastrointestinal adverse events following a therapy administered by the sublingual route should be reported as systemic rather than local adverse events. There were no reports of serious adverse systemic events nor anaphylaxis and no recorded use of adrenaline in any of the studies.

Quality of life

Quality of life was reported by three studies, but assessment in those studies differed greatly, and we considered that these data could not be included in our analysis.

Discussion

This systematic review of sublingually administered allergen immunotherapy (SLIT) represents an update of a review first published in *The Cochrane Library* in 2003 (3). The original review included data from 22 randomized controlled trials (979 patients) and demonstrated the efficacy of this form of treatment based on meta-analysis of symptom severity scores (SMD -0.42 ; 95% confidence interval (CI) -0.69 to -0.15). Ongoing research in this area has been considerable, and this review has now been updated to include studies published since 2003. The number of studies included has almost trebled to 60 (with 49 being suitable for pooling in meta-analyses), and the number of patients in meta-analysis has increased over four-fold, reflecting a trend towards larger, better-designed and more powerful trials.

The overall results of the meta-analysis differ little from those seen in 2003, with the overall effect for symptom scores SMD (-0.49 ; 95% CI -0.64 to -0.34) being of a similar

Table 1 Subgroup analyses – symptom scores

Subgroup	Number of studies	<i>n</i> (active)	<i>n</i> (placebo)	SMD (95% CI)	<i>P</i>
Allergen					
All seasonal	39	2081	2003	−0.34 (−0.44; −0.25)	<0.00001
All perennial	10	252	253	−0.93 (−1.69; −0.17)	<0.00001
Grass	23	1549	1464	−0.35 (−0.45; −0.24)	<0.00001
Parietaria	5	74	77	−0.36 (−0.69; −0.04)	0.03
Ragweed	2	85	90	−0.44 (−0.74; −0.14)	0.004
Tree	9	197	183	−0.42 (−0.77; −0.06)	0.02
House dust Mite	9	232	232	−0.97 (−1.8; −0.3)	0.02
Age					
Adults	34	1631	1566	−0.44 (−0.56; −0.31)	0.0001
Children	15	702	690	−0.52 (−0.94; −0.1)	0.02
Treatment duration					
<6 months	17	890	882	−0.54 (−0.86; −0.21)	0.001
6–12 months	16	867	869	−0.31 (−0.46; −0.16)	<0.0001
>12 months	16	580	509	−0.63 (−0.92; −0.34)	<0.0001
Dose of major allergen					
<5 µg	8	141	134	−0.32 (−0.65; 0.05)	0.09
5–20 µg	12	1006	966	−0.34 (−0.43; −0.24)	<0.00001
>20 µg	12	541	500	−0.33 (−0.49; −0.17)	<0.00001
Formulation					
Drops	35	1270	1194	−0.35 (−0.42; −0.28)	<0.00001
Tablets	11	945	936	−0.48 (−0.58; −0.38)	<0.00001

SMD, standardized mean difference.

magnitude, with tighter CI reflecting the greatly increased number of study subjects. The same is true for the analysis of medication scores, with SMD −0.32 (95% CI −0.43 to −0.21). These data continue to support the clinical efficacy of SLIT for allergic rhinitis.

In contrast to the original review, the greater number of studies has allowed more meaningful analyses of some of the predetermined subgroups. In particular, there are now 15 studies looking exclusively at children, some of which are large studies in their own right (16, 69). The treatment effect within this subgroup of trials appears to be similar to that seen in adults, especially when considering symptom scores. SLIT represents a particularly attractive alternative to injection immunotherapy in this patient group and our findings are entirely consistent with those reported elsewhere (72).

The protocol for the original review reflected the then classification of aero-allergens into seasonal and perennial. The Allergic Rhinitis and its Impact on Asthma classification (73) now uses the terms intermittent and persistent, but for this review this change makes no difference. In this meta-analysis, there does appear to be a greater effect with perennial allergens (predominantly house dust mite) when compared to seasonal allergens although this is based on fewer studies. More studies of perennial rhinitis are needed to confirm or exclude this possibility.

It is not possible to differentiate between different doses on the basis of this meta-analysis. The difficulty in determining dose in terms of micrograms of major allergen and standardizing this information across a range of studies utilizing allergen extracts from different sources was acknowledged in the original review and remains problematic.

Although the difference is small, this review has shown a trend in symptom score reduction in trials that lasted for longer than 12 months, when compared with shorter treatment periods. Indeed, SLIT is now given for longer time periods (over 12 months in 32% of included studies compared with 19% in 2003). More recent studies have shown that treatment for longer than 12 months provides consistent clinical improvement in symptom and medication scores (74, 75). These data are encouraging and should be taken into consideration in future recommendations or guidelines for the use of SLIT in allergic rhinitis.

Looking at the total effect and SMD (95% CI) of SLIT for individual allergens, house dust mite appears to be more effective than treatment with other types of allergen and even more effective than treatment with grass pollen. However, the majority of these trials are small, with five (out of nine) trials involving fewer than 20 participants. Heterogeneity in this group is amongst the highest in all the meta-analyses; when comparing *P*-values for the overall effect, the level of significance appears to be lower than for the majority of

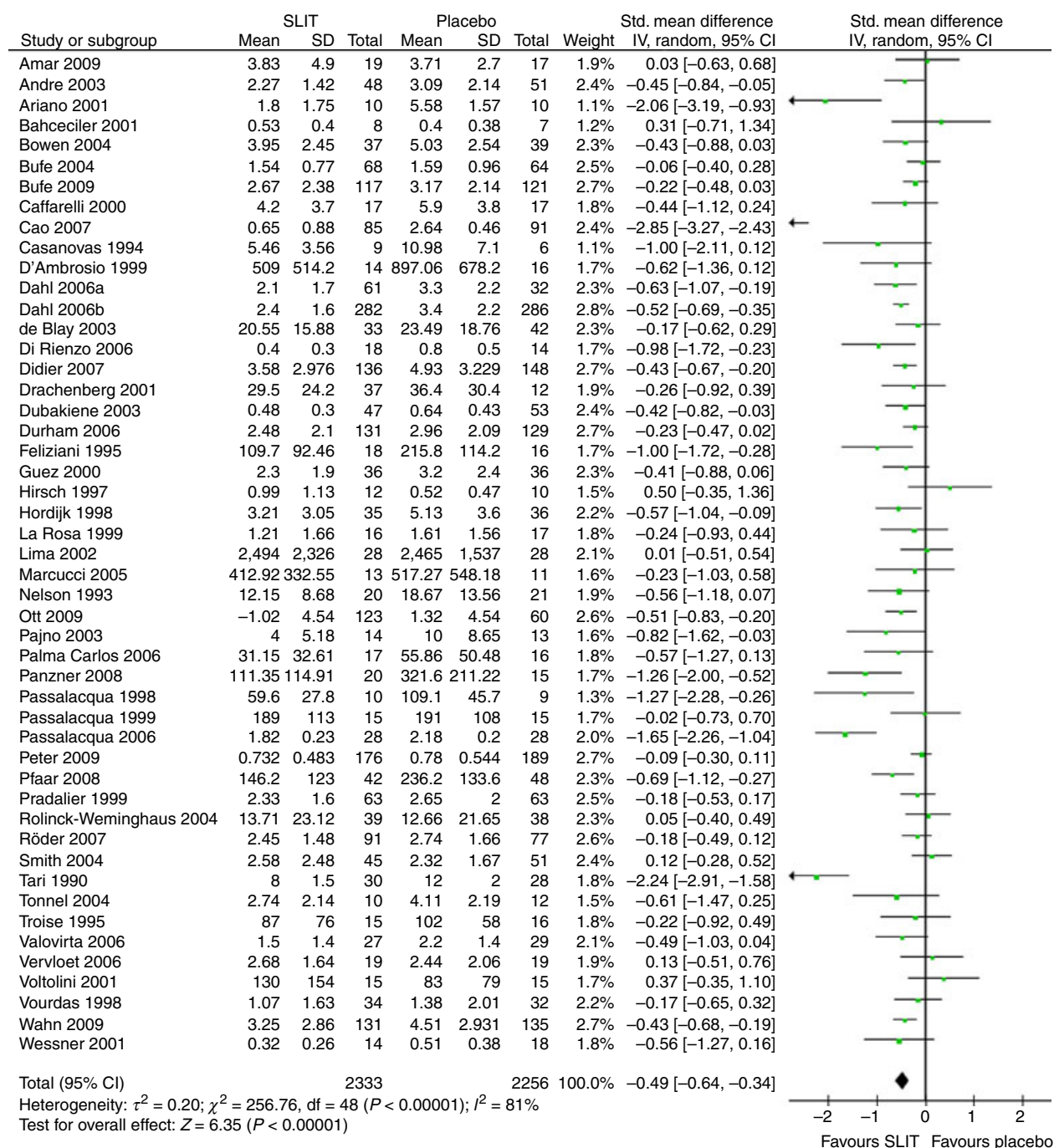


Figure 2 Symptom scores-all.

other allergens. We therefore conclude that this finding should be interpreted with caution.

This review has shown that SLIT provokes significant changes in terms of allergen-specific IgG and IgG4 antibodies, which coincide with a clinical response in terms of symptom and medication scores. These findings are in complete concordance with the findings of the previous SLIT review (3), as well as injection immunotherapy (76).

Unfortunately, changes detected in IgG and IgG4 values were not supported by changes in allergen sensitivity, and meta-analysis of data for skin and nasal reactivity after treatment showed no difference between the immunotherapy and placebo group (5).

The exact role of IgG and IgG4 antibodies is still not completely clear. Although they are likely to have a 'protective' role, there is still an ongoing debate as to whether this

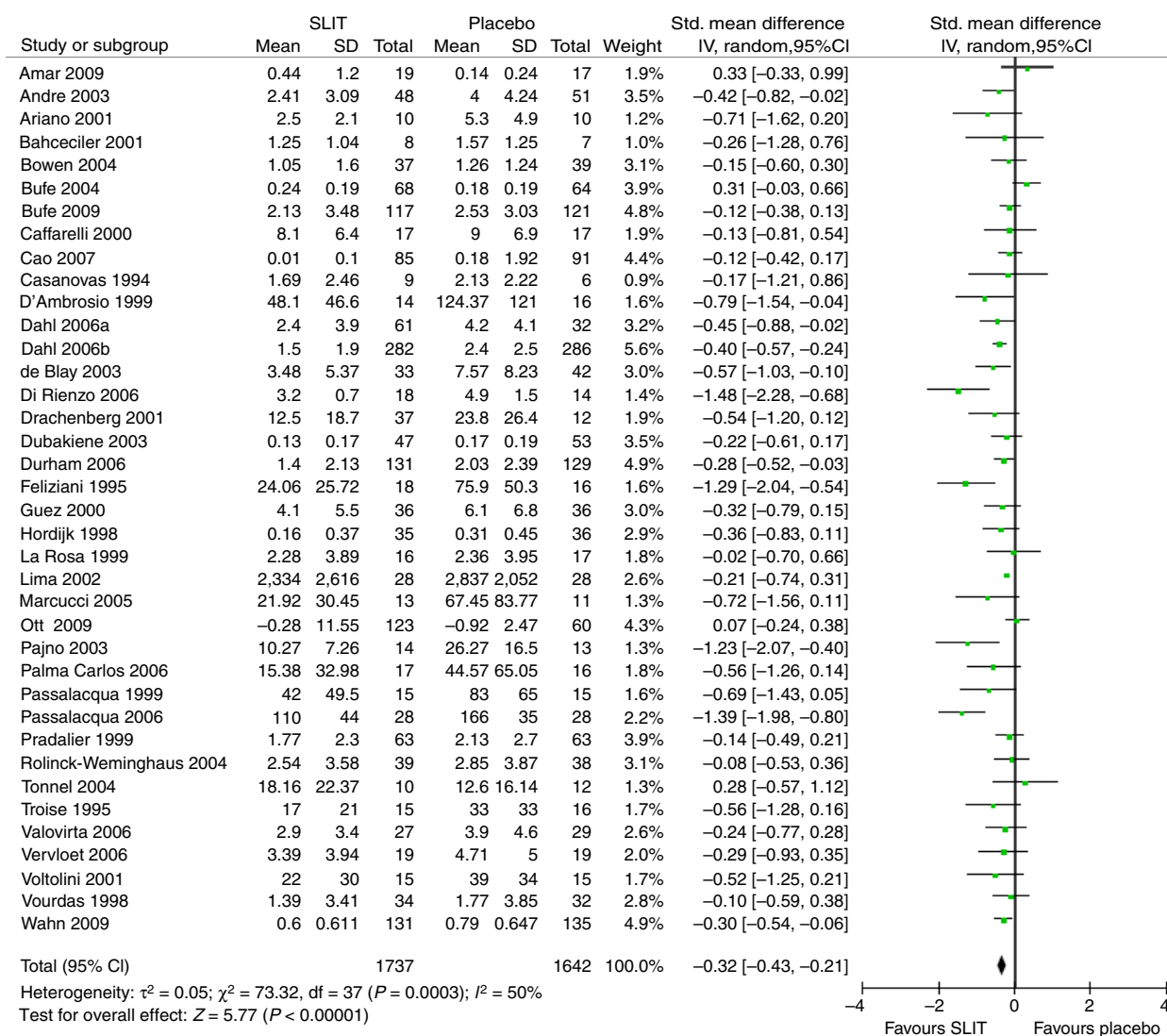


Figure 3 Medication scores-all.

increase in (particularly) IgG4 is just a consequence of exposure to a high dose of allergen or the real immunomodulatory effect of SLIT. This review could not draw a definitive conclusion and only further mechanistic studies can enable us to answer this question.

This review explored the possible differences between different sublingual preparations (i.e. sublingual drops vs tablets). Although tablets proved to be more effective in terms of medication scores and had similar efficacy in terms of symptoms, overlapping CI and the substantial heterogeneity between studies did not allow us to draw any firm conclusions. It seems both preparations are similarly effective.

An increasing number of studies report quality of life as a primary or secondary outcome measure as is the case in clinical trials in general. Nevertheless, there were big differences in quality-of-life scoring systems such that we were unable to analyse these data by meta-analysis.

It was acknowledged in the original review that many of the studies included were small, early publications that did not conform to the CONSORT (1996) guidelines for the publication of randomized controlled trials (77, 78). The methodological quality of the studies included on this occasion has been scrutinized more closely using the new Cochrane criteria, including assessment of randomization and allocation concealment. The possible confounder of publication bias that exists in all meta-analysis (72, 79) was acknowledged in the original review and has again been addressed on this occasion through extensive consultation with those active in the field of SLIT research. We are confident that no data have been excluded purely on the basis of negative outcome.

Heterogeneity between studies was acknowledged as a significant problem in the last review and is a known problem in systematic reviews. This results largely from methodological and clinical heterogeneity (i.e. differences in scoring

Table 2 Subgroup analyses – medication scores

Subgroup	Number of studies	<i>n</i> (active)	<i>n</i> (placebo)	SMD (95% CI)	<i>P</i>
Allergen					
All seasonal	32	1557	1457	−0.3 (−0.41; −0.19)	<0.00001
All perennial	6	180	185	−0.43 (−0.89; 0.02)	0.06
Grass	17	1201	1107	−0.23 (−0.37; −0.1)	0.0008
Parietaria	5	74	77	−0.62 (−1; −0.24)	0.001
Ragweed	2	85	90	−0.3 (−0.6; 0)	0.05
Tree	9	197	183	−0.38 (−0.62; −0.13)	0.002
House dust mite	5	95	94	−0.52 (−1.09; −0.03)	0.07
Age					
Adults	26	1168	1067	−0.4 (−0.53; −0.26)	<0.00001
Children	12	569	575	−0.16 (−0.32; 0)	0.06
Treatment duration					
<6 months	15	694	672	−0.32 (−0.43; 0.18)	<0.00001
6–12 months	13	705	693	−0.31 (−0.5; −0.12)	0.002
>12 months	10	338	277	−0.34 (−0.62; −0.04)	0.03
Dose of major allergen					
<5 µg	6	110	109	−0.59 (−0.94; 0.24)	0.0008
5–20 µg	11	992	948	−0.21 (−0.35; −0.07)	0.003
>20 µg	10	360	301	−0.22 (−0.43; 0)	0.05
Formulation					
Drops	27	865	788	−0.01 (−0.05; 0.04)	0.74
Tablets	9	799	779	−0.33 (−0.46; −0.2)	<0.00001

SMD, standardized mean difference.

Table 3 Adverse events

Type of reaction	Studies	Sublingual immunotherapy		Placebo	
		Patients	Total events (per patient)	Patients	Total events (per patient)
Local					
Labial oedema	11	604	55 (0.09)	536	7 (0.01)
Buccal pruritis	21	1126	1798 (1.6)	1075	492 (0.46)
Buccolingual oedema	8	648	143 (0.22)	606	2 (0.003)
Throat irritation	10	770	243 (0.3)	747	29 (0.04)
Oral (nonspecified)	3	68	143 (2.1)	71	24 (0.34)
Local nonspecified	3	119	7 (0.06)	116	3 (0.03)
Systemic					
Urticaria	8	204	7 (0.03)	199	9 (0.04)
Pruritis/rash	10	363	13 (0.04)	222	9 (0.04)
Conjunctivitis	8	262	774 (2.95)	238	786 (3.3)
Rhinitis	16	965	1403 (1.45)	912	1034 (1.13)
Rhinoconjunctivitis	6	184	60 (0.33)	176	58 (0.33)
Asthma/wheeze	15	488	51 (0.1)	450	42 (0.09)
Cough	8	337	313 (0.93)	304	211 (0.69)
Gastrointestinal	20	630	88 (0.14)	561	10 (0.02)
Headache	6	535	70 (0.2)	548	68 (0.12)
Anaphylaxis	6	291	0	288	0
Systemic nonspecified	5	330	4 (0.01)	36	0

systems, sample sizes, type and dose of allergen, age groups, etc.) used across studies. Selection of the studies for this review was defined in our protocol, and studies that satisfied

our criteria were chosen. The method used by The Cochrane Collaboration for assessing heterogeneity has however changed and can now be expressed as an I^2 statistic. It remains

the case that studies in this field are heterogeneous, and data are expressed in a wide variety of different ways. However, certain subgroup analyses (e.g. seasonal allergens, individual allergens, subgroup analysis for major allergen content) have shown the significant reduction in heterogeneity even though these groups were prespecified by a protocol. This means that there will always be a degree of interpretation required when amalgamating studies in meta-analysis, and further subgroup analysis could be performed to address better the problem of heterogeneity. Despite this, there is remarkable consistency in the outcomes of related systematic reviews (3, 80, 81).

Adverse events

Although considered as a secondary outcome, we felt analysis of adverse events to be crucial as a low incidence confers advantage on SLIT as an alternative to injection immunotherapy. Adverse events data were, by their nature, noncontinuous. Authors mainly reported data as total number of events for a number of patients, rather than number of certain events per patient. Some papers reported their most common events as a percentage of total events or as a percentage of patients who experienced particular events. These were therefore not suitable for meta-analysis, and we were able to perform only descriptive analysis. A further problem is that, unlike for the subcutaneous route, there is currently no internationally standardized methodology for reporting local adverse events associated with SLIT. With these reservations, local reactions are again shown to be common and reported much more frequently in SLIT recipients than in those receiving placebo. These are clearly unavoidable but are usually seen as an inconvenience and cause little distress and have no lasting effect; though, rarely these adverse events were distressing enough to warrant withdrawal of treatment.

Systemic reactions were again largely confined to the upper respiratory tract and associated organs (rhinitis, conjunctivitis or rhinoconjunctivitis) and were more frequent in the SLIT than in the placebo groups. Asthma or wheeze was no more likely in SLIT recipients than in placebo recipients. Gastrointestinal effects (nonspecified) were uncommon but more

apparent in SLIT recipients and were largely confined to paediatric trials. None were considered serious. There were no reports in clinical trials of severe systemic reactions or anaphylaxis, and none of the systemic reactions needed the use of adrenaline. No fatalities were reported.

This review evaluates a large number of double-blind, placebo-controlled studies that, in total, give us a large number of doses. No incidences of life-threatening reactions were reported in the studies analysed. We conclude that SLIT remains a safe treatment with an extremely low incidence of significant side-effects. We have been unable to correlate adverse events with allergen dose.

There are no reports of fatalities following SLIT. Six isolated cases of severe reactions have been reported independently of clinical trials and all involved deviation from current recommended practice according to international guidelines (82–86). Numbers are too few to allow identification of risk factors for severe systemic reactions; however, it can be noted that five out of six occurred in young women, five out of six had asthma, and two out of six had previously experienced severe reactions during subcutaneous immunotherapy. These data should be viewed in the context of the number of doses of SLIT that have been prescribed and administered worldwide.

Since the original systematic review in 2003, SLIT has become established as an effective and low-risk alternative to allergen injection immunotherapy, which carries a significant morbidity and a requirement for delivery within specialist centres capable of meeting CSM recommendations. SLIT is recommended to be initiated in secondary care and the first dose taken under medical supervision, whereas maintenance treatment is recommended to be self-administered in the patient's home.

Only two studies in the original review compared injection immunotherapy with SLIT directly (87, 88). In the current review, only one study compared injection immunotherapy vs SLIT. Although comparison of those two treatment options was not the objective of this review, the search process enabled us to identify papers comparing the efficacy of these treatment options. We found very few such papers: there

Table 4 Cochrane systematic reviews for Efficacy and Safety of Immunotherapy

	Authors	Age group	N participants active/placebo N for symptom score (medication score)	Symptom Scores SMD random (95% CI) <i>P</i> value heterogeneity (<i>I</i> ²)	Medication Scores SMD random (95% CI) <i>P</i> value heterogeneity (<i>I</i> ²)
SLIT	Radulovic et al. (5)	Adults and children	2333/2256 (1737/1642)	−0.49 (−0.64, −0.34) <i>P</i> < 0.00001 <i>I</i> ² = 81%	−0.32 (−0.43, −0.21) <i>P</i> < 0.00001 <i>I</i> ² = 50%
SCIT	Calderon et al. (76)	Adults	597/466 (549/414)	−0.73 (−0.97, −0.50) <i>P</i> < 0.00001 <i>I</i> ² = 63%	−0.57 (−0.82, −0.33) <i>P</i> < 0.00001 <i>I</i> ² = 64%
	Abramson et al. (89)	Adults and children	727/557 (485/384)	−0.59 (−0.83, 0.35) <i>P</i> < 0.00001 <i>I</i> ² = 73%	−0.53 (−0.80, −0.27) <i>P</i> = 0.000065 <i>I</i> ² = 67%

Heterogeneity: low = *I*²25%; moderate = *I*²50%; high = *I*²75%.

SMD, standardized mean difference; SLIT, sublingual immunotherapy.

appears to be insufficient data available to draw any conclusions and more definitive head-to-head trials are needed.

A Cochrane review of allergen injection immunotherapy, which included 51 trials with 2871 participants (76), showed a SMD of -0.73 (95% CI -0.97 to -0.5) for symptom scores compared with placebo and a SMD of -0.57 (95% CI -0.82 to -0.33) for medication scores. Although the SMDs are numerically different, the CI overlap with those for SLIT, indicating no apparent difference between the two therapies on this basis. However, it is not correct to perform a direct statistical comparison between these two meta-analyses. These data raise the importance of future double-blind, double-dummy trials that directly compare these two routes of immunotherapy.

With similar reservations, the latest Cochrane review of subcutaneous immunotherapy for asthma (89) has shown levels of efficacy of the same order in terms of reduction of symptom scores and need for rescue medication (Table 4).

Conclusion

The original systematic review by Wilson et al. (3) changed the field of SLIT for allergic rhinitis – encouraging significant investment in the further evaluation of a treatment with proven efficacy. This latest review includes the subsequent highly powered clinical trials and includes more than four times the number of patients. The data establish SLIT as a viable alter-

native to allergen injection immunotherapy, with a significantly lower risk profile. There is support for the use of SLIT in children and additional support for its use in allergic rhinitis because of seasonal allergens and perennial disease because of house dust mite. The sublingual route appears safer and has a better side-effect profile compared to the subcutaneous route, although a standardized grading system for side-effects is needed to permit more accurate and consistent reporting in the future. A recent study of SLIT using grass allergen tablets for seasonal pollinosis demonstrated long-term benefit for at least one year following 3 years of treatment (75), implying the induction of both clinical and immunological tolerance. Further long-term studies in adults and children are needed; also adequately powered head-to-head trials of sublingual vs subcutaneous immunotherapy. Inclusion of standardized quality-of-life measures and pharmacoeconomic evaluations as major outcomes will further define the place of SLIT in the treatment of allergic rhinoconjunctivitis.

Conflicts of interest

SR Durham has received lecture and consultancy fees and research funding via Imperial College from ALK Abello, Horsholm Denmark, a manufacturer of allergy vaccines. Moises Calderon has received lecture fees from ALK Abello, Horsholm Denmark, a manufacturer of allergy vaccines.

References

- Calderon M, Mösges R, Hellmich M, Demoly P. Towards evidence-based medicine in specific grass pollen immunotherapy. *Allergy* 2010;**65**:420–434.
- Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;**341**:468–475.
- Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2003; Art. No.: CD002893. DOI: 10.1002/14651858.CD002893.
- Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;**60**:4–12.
- Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010; Art. No.: CD002893. DOI: 10.1002/14651858.CD002893.pub2
- Clarke M, Oxman A, eds. Cochrane Reviewers' Handbook 4.2.0 [updated March 2003]. The Cochrane Library [Issue 2]. Oxford: Update Software.
- Moher D, Ba' Pham, Jones A, Cook DJ, Jadad AR, Moher M et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**:609–613.
- Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2008. Available from <http://www.cochrane-handbook.org>.
- The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.
- Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in multiallergen extract. *J Allergy Clin Immunol* 2009;**124**:150–156.
- Andre C, Perrin-Fayolle M, Grosclaude M, Couturier P, Basset D, Cornillon J et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with standardized ragweed extract in patients with seasonal rhinitis. *Int Arch Allergy Immunol* 2003;**131**:111–118.
- Ariano R, Spadolini I, Panzani RC. Efficacy of sublingual immunotherapy in Cupressaceae allergy using an extract of Cupressus arizonica. A double blind study. *Allergol Immunopathol* 2001;**29**:238–244.
- Bahceciler NN, Isik U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double blind, placebo-controlled study. *Pediatr Pulmonol* 2001;**32**:49–55. Published and unpublished data.
- Bowen T, Greenbaum J, Charbonneau Y, Hebert J, Filderman R, Sussman G et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004;**93**:425–430. Published and unpublished data.
- Bufe A, Ziegler-Kirbach E, Stoeckman E, Heidemann P, Gehlhar K, Holland-Letz T et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms, a double-blind, placebo-controlled study. *Allergy* 2004;**59**:498–504. Published and unpublished data.
- Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;**123**:167–173.e7. Published data only (unpublished sought but not used)
- Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy* 2000;**55**:1142–1147. Published and unpublished data.
- Calderon M, Essendrop M. Specific immunotherapy with high dose SQ standardized

- grass allergen tablets was safe and well tolerated. *J Investig Allergol Clin Immunol* 2006;**16**:338–344.
19. Cao LF, Lu Q, Gu HL, Chen YP, Zhang Y, Lu M et al. Clinical evaluation for sublingual immunotherapy of allergic asthma and atopic rhinitis with Dermatophagoides Farinae Drops. *Zhonghua Er Ke Za Zhi* 2007;**45**: 736–741. Published and unpublished data.
 20. Casanovas M, Guerra F, Moreno C, Miguel R, Maranon F, Daza JC. Double-blind, placebo-controlled clinical trial of preseasonal treatment with allergenic extracts of Olea europaea pollen administered sublingually. *J Investig Allergol Clin Immunol* 1994;**4**: 305–314. Published and unpublished data.
 21. Clavel R, Bousquet J, Andre C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1998;**53**:493–498.
 22. Purello-D'Ambrosio F. Sublingual immunotherapy: a double-blind, placebo-controlled trial with Parietaria judaica extract standardised in mass units in patients with rhinoconjunctivitis, asthma, or both. *Allergy* 1999;**54**:968–973. Published and unpublished data.
 23. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;**61**:185–190.
 24. Dahl R, Kapp A, Colombo G, de Monchy JGR, Rak S, Emminger W et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;**118**:434–440.
 25. de Blay F, Purohit A, Kanny G, Le Sellin J, Wessel F, Leynadier F et al. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind placebo controlled study [Abstract]. In: XXII Congress of the European Academy of Allergology and Clinical Immunology (EAACI). 2003:780. Published and unpublished data.
 26. Di Rienzo V, Pucci S, D'Alo S, Di Cara G, Incorvaia C, Frati F et al. Effects of high-dose sublingual immunotherapy on quality of life in patients with cypress-induced rhinitis: a placebo-controlled study. *Clin Exp Allergy Rev* 2006;**6**:67–70. Published and unpublished data.
 27. Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;**120**:1338–1345.
 28. Drachenberg KJ, Pfeiffer P, Urban E. Sublingual immunotherapy – results from a multi-centre, randomised, double-blind, placebo-controlled study with a standardised birch and grass/rye pollen extract. *Allergologie* 2001;**24**:525–534.
 29. Dubakiene R, Kleinjans HAJ. Effectiveness of specific sublingual IT (SLIT) with tree pollen. A placebo controlled study in 119 patients [Abstract]. In: XXII Congress of European Academy of Allergology and Clinical Immunology. 2003. Published and unpublished data.
 30. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;**117**:802–809. Published and unpublished data.
 31. Feliziani V, Lattuada G, Parmiani S, Dal'Aglio PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. *Allergologia et Immunopathologia (Madrid)* 1995;**23**: 224–230. Published and unpublished data.
 32. Grosclaude M, Bouillot P, Alt R, Leynadier F, Scheimann P, Rufin P et al. Safety of various dosage regimens during induction of sublingual immunotherapy: a preliminary study. *Int Arch Allergy Immunol* 2002;**129**:248–253.
 33. Guez S, Vatrinet C, Fadel R, Andre C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000;**55**:369–375. Published and unpublished data.
 34. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol* 1997;**8**:21–27. Published and unpublished data.
 35. Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a standardised grass pollen extract: a double-blind, placebo-controlled study. *Allergologia et Immunopathologia (Madrid)* 1998;**26**: 234–240.
 36. Ibañez MD, Kaiser F, Knecht R, Armentia A, Schöpfer H, Tholstrup B et al. Safety of specific sublingual immunotherapy with SQ standardized grass allergen tablets in children. *Pediatr Allergy Immunol* 2007;**18**: 516–522.
 37. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S et al. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003;**14**:216–221.
 38. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;**59**:45–53.
 39. Kleine-Tebbe J, Ribel M, Herold DA. Safety of SQ-standardized grass allergen tablet for sublingual immunotherapy: a randomized, placebo controlled trial. *Allergy* 2006;**61**:181–184.
 40. La Rosa M, Ranno C, Andre C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999;**104**:425–432. Published and unpublished data.
 41. Lima M, Wilson DR, Roberts A, Walker SM, Durham SR. Grass pollen sublingual immunotherapy (SLIT) for seasonal rhinoconjunctivitis: a randomised controlled trial. *Clin Exp Allergy* 2002;**32**:507–514. Published and unpublished data.
 42. Malling HJ, Lund L, Ipsen H, Poulsen L. Safety and immunological changes during sublingual immunotherapy with standardized quality grass allergen tablets. *J Investig Allergol Clin Immunol* 2006;**16**:162–168. Published and unpublished data.
 43. Marcucci F, Sensi L, Di Cara G, Salvatori S, Bernini M, Pecora S et al. Three-year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing sublingual immunotherapy. *Pediatr Allergy Immunol* 2005;**16**: 519–526.
 44. Marcucci F, Sensi L, Frati F, Bernardini R, Novembre E, Barbato A et al. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. *Allergy* 2003;**58**:657–662.
 45. Nelson HS, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1993;**92**:229–236.
 46. Ott H, Sieber J, Brehler R, Fölster-Holst R, Kapp A, Klimek L et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 2009;**64**:179–186.
 47. Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy* 2003;**33**:1641–1647. Published and unpublished data.
 48. Palma-Carlos AG, Santos AS, Branco-Ferreira M, Pregal AL, Palma-Carlos ML, Bruno ME et al. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitis patients. A double-blind, placebo-

- controlled study. *Allergologia et Immunopathologia (Madrid)* 2006;**34**:194–198. Published and unpublished data.
49. Panzner P, Petrás M, Šýkora T, Lesná I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. *Respir Med* 2008;**102**: 1296–1304. Published and unpublished data.
 50. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998;**351**:629–632. Published and unpublished data.
 51. Passalacqua G, Albano M, Riccio A, Fregonese L, Puccinelli P, Parmiani S et al. Clinical and immunologic effects of a rush sublingual immunotherapy to Parietaria species: a double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 1999;**104**: 964–968. Published and unpublished data.
 52. Passalacqua G, Pasquali M, Ariano R, Lombardi C, Giardini A, Baiardini I et al. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy* 2006;**61**:849–854. Published and unpublished data.
 53. Peter R, Kleinjans H, Hecker H. Significant increase in IgG(4) levels after slit grass treatment. A double-blind, placebo-controlled, multi-center study (twin grasses study). *Allergy* 2009;**90**:352–353. Published and unpublished data.
 54. Pfaar O, Klimek L. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol* 2008;**100**:256–263. Published and unpublished data.
 55. Pradaliere A, Basset D, Claudel A, Couturier P, Wessel F, Galvain S et al. Sublingual-swallow immunotherapy (SLIT) with a standardised five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999;**54**:819–828.
 56. Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhino-conjunctivitis to grass pollen. *Allergy* 2004;**59**:1285–1293. Published and unpublished data.
 57. Röder E, Berger MY, Hop WC, Bernsen RM, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol* 2007;**119**:892–898. Published and unpublished data.
 58. Sabbah A, Hassoun S, Le Sellin J, Andre C, Sicard H. A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy* 1994;**49**:309–313.
 59. Sanchez Palacios A, Schamann F, Garcia JA. Sublingual immunotherapy with cat extract, personal experience. *Allergologia et Immunopathologia (Madrid)* 2001;**29**:60–65.
 60. Smith H, White P, Annila I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004;**114**:831–837.
 61. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite: a double-blind study. *Allergologia et Immunopathologia (Madrid)* 1990;**18**:277–284. Published and unpublished data.
 62. Tari MG, Mancino M, Madonna F, Buzzoni L, Parmiani S. Immunologic evaluation of 24 month course of sublingual immunotherapy. *Allergologia et Immunopathologia* 1994;**22**:209–216.
 63. Tonnel AB, Scherpereel A, Douay B, Mellin B, Leprince D, Goldstein N et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004;**59**:491–497. Published and unpublished data.
 64. Troise C, Voltolini S, Canessa A, Pecora S, Negrini AC. Sublingual immunotherapy in Parietaria pollen-induced rhinitis: a double-blind study. *J Investig Allergol Clin Immunol* 1995;**5**:25–30. Published and unpublished data.
 65. Valovirta E, Jacobsen L, Ljorring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy* 2006;**61**:1177–1183.
 66. Vervloet D, Birnbaum J, Laurent P, Hugues B, Fardeau MF, Massabie-Bouchat YP et al. Safety and efficacy of Juniperus Ashei sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis: a double-blind, placebo-controlled study. *Int Arch Allergy Immunol* 2007;**142**:239–246.
 67. Voltolini S, Modena P, Minale P, Bignardi D, Troise C, Puccinelli P et al. Sublingual immunotherapy in tree pollen allergy. Double-blind, placebo-controlled study with a biologically standardised extract of three pollens (alder, birch and hazel) administered by a rush schedule. *Allergologia et Immunopathologia (Madrid)* 2001;**29**:103–110. Published and unpublished data.
 68. Vourdas D, Syrigou E, Potamianou P, Carat F, Batard T, Andre C et al. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 1998;**53**:662–672. Published and unpublished data.
 69. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;**123**:160–166.e3. Published and unpublished data.
 70. Wessner DB, Wessner S, Mohrschlager M, Rakoski J, Ring J. Efficacy and safety of sublingual immunotherapy in adults with allergic rhinoconjunctivitis: results after 2 years of controlled trial [Abstract]. *Allergy* 2001;**56**(Suppl 68):88. Published and unpublished data.
 71. Wutrich B, Bucher C, Jorg W, Bircher A, Eng P, Schneider Y et al. Placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Investig Allergol Clin Immunol* 2003;**13**:145–148. Published and unpublished data.
 72. Calderon MA. Meta-analyses of specific immunotherapy trials. *Drugs Today (Barc)* 2008;**44**(Suppl B):31–34.
 73. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**(Suppl 86): S8–S160.
 74. Dahl R, Kapp A, Colombo G, De Monchy JG, Rak S, Emminger W et al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol* 2008;**121**: 512–518.
 75. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010;**125**:131–138.e1–7.
 76. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007, Art. No.: CD001936. DOI: 10.1002/14651858.CD001936.pub2.
 77. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;**276**:637–639.
 78. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of

- parallel-group randomised trials. *Lancet* 2001;**14**:1191–1194.
79. Nieto A, Mazon A, Pamies R, Bruno L, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. *J Allergy Clin Immunol* 2009;**124**: 157–161.e1–32.
 80. Casale TB, Canonica GW, Bousquet J, Cox L, Lockey R, Nelson HS et al. Recommendations for appropriate sublingual immunotherapy clinical trials. *J Allergy Clin Immunol* 2009;**124**:665–670.
 81. Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006; **117**:1021–1035.
 82. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy* 2006;**61**:1236–1237.
 83. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy* 2008;**63**:374.
 84. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009;**64**:963–964.
 85. Dunskey EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. *Allergy* 2006;**61**:1235.
 86. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 2007;**62**:567–568.
 87. Mungan D, Misirligil Z, Gürbüz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma-a placebo controlled study. *Ann Allergy Asthma Immunol* 1999;**82**:485–490.
 88. Quirino T, Lemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin Exp Allergy* 1996;**26**:1253–1261.
 89. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010; Art. No.: CD001186. DOI: 10.1002/14651858. CD001186.pub2.