Original Article

Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis

J.M. Olaguíbel, M.J. Álvarez Puebla

Sección de Alergología. Hospital Virgen del Camino. Pamplona. Spain

Summary. *Background.* Sublingual route, that allows the safe administration of allergen vaccination at home and without injections, is a highly attractive alternative to parenteral delivery, especially among the youngest population. However, its efficacy in children has been questioned.
Objective. To evaluate the efficacy (symptom and medication scores) of sublingual allergen vaccination compared to placebo in paediatric patients.
Search strategy: MEDLINE, EMBASE, ISI and the Cochrane Central Register of Controlled Trials were explored (completed in January/04) for potentially relevant studies.
Selection criteria: Randomized double-blind placebo-controlled clinical trials involving children ≤ 14 years-old with either rhinitis or asthma of proved allergic aetiology.
Data collection and analysis. Two reviewers analyzed independently the eligibility of studies for inclusion. The combined standardized mean difference (SMD) method was used to evaluate differences. Since heterogeneity was expected, probably due to the different procedures from each trial, we used the random effect model to obtain SMD. However, we also present the SMD values from the fixed effect model. The main outcomes were clinical symptom (asthma, rhinitis and conjunctivitis) and drug requirement scores. Safety, immunological and clinical changes were also reviewed.
Results. Seven double-blind placebo-controlled trials, enrolling 256 children (129 treatment and 127 placebo recipients), were analyzed. We observed decreases in symptom (SMD: -1.42 for asthma, -0.44 for rhinitis and -1.49 for conjunctivitis) and medication requirement (SMD: -1.01) scores. Only reductions in asthma (p=0.01) and drug dosage (p=0.06) scores reached statistical significance with the random effect model but changes in rhinitis symptoms (p=0.27) or conjunctival symptoms (p=0.19) were not statisticaly significant. Results obtained with the fixed effect model were similar in magnitude (SMD: –1.60 for asthma, SMD: –0.47 for rhinitis, SMD: –1.09 for conjunctivitis and, SMD: –0.54 for drug intake). Safety was a constant in all the studies; neither severe nor systemic reactions were observed and, oral and gastrointestinal complains were the most common adverse effects.
Conclusion: In children, sublingual delivery of allergen vaccination constitutes a safe and effective alternative to the sublingual route to reduce allergy respiratory symptoms and drug intake. Further studies in this group of age are required to establish the optimal conditions for sublingual allergen vaccination.

Key words: Sublingual allergen vaccination, immunotherapy, rhinitis, asthma, children, efficacy, meta-analysis.

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Introduction

Allergen vaccination (AV) is the only treatment capable of modifying the natural history of respiratory allergic diseases [1]. Its mechanism of action, not completely elucidated, probably consists in redirecting the immune response towards a reduction in Th2 cytokines [2]. Although small [3], the potential risk of severe systemic side effects, including anaphylaxis, has even lead to some specialists from UK to consider asthma as a contraindication for subcutaneous AV [4]. On the other hand, the World Health Organization recommends to administer this treatment "under close supervision of a trained physician who can recognize early symptoms and signs of anaphylaxis and administer emergency treatment" [5] which gives rise to considerable health and social costs [6]. Secondly, up to 20-30% of patients receiving aluminium-containing AV can develop subcutaneous nodules [7] that although not dangerous, result unattractive, disturbing and annoying to the patients. These data, together with the reluctance that some patients, especially children, show to receive injections, support a role for the new routes of administering AV.

Sublingual allergen vaccination (SLAV) is a viable alternative to the subcutaneous route, whose efficacy and safety has been shown by randomized clinical trials [5, 8]. However, some authors have stressed the need of having of well designed, large-scale and placebo-controlled clinical trials before attributing a role in respiratory allergy treatment to SLAV [9]. This assertion would be important in children since one recent meta-analysis [10] reported the failure of SLAV in improving rhinitis symptoms in this group of age. We have addressed the present study to evaluate, from data obtained from published clinical trials, the efficacy and safety of SLAV among children with respiratory allergy.

Material and methods

MEDLINE, EMBASE, ISI and the Cochrane Central Register of Controlled Trials Scisearch were used to identify the clinical trials (conclusion date: January, 2004), using the search terms (Asthm*, Rhin* or hay fever) AND (Immunotherap*, vacunat* or desensitiz*) AND (sublingual). Reference lists of recent reviews and published trials were searched, too. Our criteria for considering studies in the analysis were the following:

- Randomized double-blind placebo-controlled clinical trials.
- Paediatric population (≤ 14 years-old).
- Diagnosed with either rhinitis or asthma with or without conjunctivitis. The implication of the allergen had to be proven by both clinical history and either skin prick test or serum specific IgE measurement.
- Patients had no other clinically significant allergen sensitization.
- The proper allergen was administered by the sublingual route (swallowed or not).

The types of results were classified into primary outcomes (symptom: nasal, ocular and bronchial; and drug intake scores) and secondary outcomes (safety, changes in skin reactivity and in serum immunoglubulins: IgE or IgG).

Selected articles were evaluated for methodological quality in order to be included in the meta-analysis. Inclusion of studies in the revision was decided by two of the reviewers. Further information was sought from study authors when needed.

Data analysis

RevMan 4.1 was used to analyse the data obtained from the selected studies. Although symptom and medication scores are measured using continuous data,

Table 1. Synopsis of the clinical trials included in the analysis.

Study	n (active/placebo)	Allergen	Duration (months)	Accumulated dose
Bahçeciler (20)	8/7	D. pter./D. far	6	560 µg Der p 1
Hirsch (21)	15/15	D. pter.	12	540 µg Der p 1
La Rosa (22)	20/21	Parietaria	24	52.5 mg Par j 1
Pajno (23)	12/12	D. pter.	12	130 µg Der p 1
Tari (24)	30/28	D. pter.	18	295 µg Der p 1
Vourdas (25)	34/32	Olive	6 + 6*	9.1 µg Ole e 1
Wüthrich (26)	10/12	Grass mix	24	140 µg group 5

* 6 months (from January to July) in two consecutive years.
Abbreviations: D. pter.: Dermatophagoides pteronyssinus; D. far.: Dermatophagoides farinae.

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Table 2. Adverse effects recorded in the groups of children receiving treatment and placebo.

Adverse event	Active group (n=129)	Placebo group (n= 127)
Local symptoms*	21++	7
Gastrointestinal complaints	23+++	1
Mild asthma	8+	1
Nonspecific symptoms	5	2
Urticaria	3	0
Rhinitis	1	1
Conjunctivitis	1	1
Number of adverse events	62	13

* Refers to labial, oral or gingival swelling or itching.
Comparison with placebo: $\chi 2$ p<0,05, ++ $\chi 2$ p<0,01, +++$\chi 2$ p<0,0001

the authors from each study used different ranges of scales and scoring systems. Therefore, analysis was performed by the method of standardized mean differences (SMD), expressing the difference in means between the active and the placebo groups in terms of units of the pooled standard deviation. Chi-square tests were performed to assess heterogeneity between studies, with a p value ≤0.1 indicating significant differences between studies. Due to the wide variability of procedures performed in each clinical trial, we presumed a large degree of heterogeneity and consequently chose firstly the random effects model that obtains summary statistics for the overall efficacy of the treatment (expressed as SMD with 95% confidence intervals). Anyway, given that it was as a sensitivity analysis, results obtained from the fixed effect model are also reported [11]. We want to remark that the random effect model does not adjust the heterogeneity, it is only a more conservative aproach when the heterogeneity exists.

Results

A total 54 clinical trials of sublingual immunotherapy were analyzed. We selected the 16 ones performed on paediatric population (all patients included ≤ 14 years-old) [12-27]. Of these 16 studies, we rejected one because comparison was made with fluticasone and the placebo group was not randomized [27], 2 [12, 13] because they only evaluated safety; 4 [14-17] because they were open (not controlled) studies and two additional ones [18, 19] because they only evaluated immunological data. We finally analyzed 7 double-blind placebo-controlled randomized clinical trials [20-26] enrolling 256 children (129 and 127 receiving SLAV and placebo respectively). We included in the analysis only published data from the studies of Tari [24], Hirsch [21], Pajno [23] and Bahceciler [20]; and published and unpublished observations requested from the authors in the cases of La Rosa et al [22], Vourdas et al [25] and Wütrich et al [26]. The individual features (number of patients, allergen, duration of treatment and cumulative doses) of the analyzed studies are listed in Table 1.

Primary outcomes

Symptom scores

Nasal symptoms (Figure 1). Rhinitis symptoms were evaluated in 6 studies [20-22, 24-26], with a total 117 and 115 children receiving SLAV and placebo respectively. The combined Standardized Mean Difference (SMD) for rhinitis symptoms was -0.44 (-1.22, 0.3; p=0.27).

Bronchial symptoms (Figure 2). They were evaluated in 5 studies [20, 21, 23-25] enrolling 99 children in the active and 94 in the placebo group. The combined SMD was -1.42 (-2.51, -0.34; p=0.010).

Ocular symptoms (Figure 3). Only two studies [24, 25] that included 64 active and 60 placebo children, included eye symptom scores. The combined SMD was -1.49 (-3.69, 0.72; p=0.19).

Medication requirement scores

Scores indicating the use of rescue antiallergic medication were included in 4 studies [20, 22, 23, 25] (Figure 4). They included a total 74 patients receiving SLAV and 72 patients receiving placebo. The combined SMD was -1.01 (-2.06, 0.04; p=0.06).

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Review: Sublingual immunotherapy in children with respiratory allergy
Comparison: 02 Nasal symptom scores
Outcome: 01 Nasal symptom scores

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Year
Tari	30	8.00 (1.50)	28	12.00 (2.00)		17.14	- 2.24 [- 2.91, -1.58)	1990
Hirsch	15	0.99 (1.13)	15	0.52 (0.47)		16.73	0.53 [- 0.20, 1.26]	1997
Vourdas	34	0.98 (1.31)	32	1.34 (1.78)		18.20	- 0.23 [- 0.71, 0.26]	1998
La Rosa	20	1.21 (1.66)	21	1.61 (1.56)		17.46	- 0.24 [- 0.86, 0.37]	1999
Bahceciler	8	0.53 (0.40)	7	0.40 (0.38)		14.68	0.31 [- 0.71, 1.34]	2001
Wüthrich	10	110.00 (21.86)	12	125.00 (21.86)		15.79	- 0.66 [-1.53, 0.21]	2003
	117		115			100.00	- 0.44 [-1.22, 0.35]	

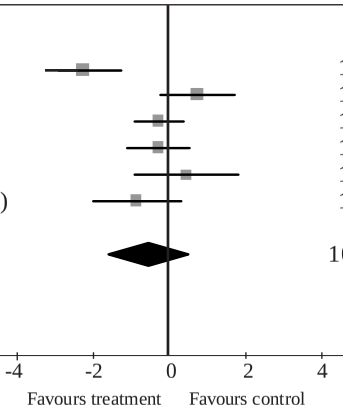

Figure 1. SLAV versus placebo for rhinitis symptoms.

Review: Sublingual immunotherapy in children with respiratory allergy
Comparison: 01 Bronchial symptom scores
Outcome: 01 Bronchial symptoms scores

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Year
Tari	30	6.00 (1.50)	28	9.70 (1.00)		20.37	- 2.84 [- 3.59, - 2.10)	1990
Hirsch	15	0.03 (0.70)	15	0.28 (0.60)		20.48	- 0.37 [- 1.10, 0.35]	1997
Vourdas	34	0.15 (0.07)	32	0.32 (0.07)		20.89	- 2.40 [- 3.04, -1.76]	1998
Pajno	12	6.00 (3.40)	12	13.20 (6.20)		19.45	- 1.39 [- 2.30, 0.48]	2000
Bahceciler	8	0.25 (0.75)	7	0.24 (0.40)		18.81	0.02 [-1.00, 1.03]	2001
	99		94			100.00	- 1.42 [- 2.51, - 0.34]	

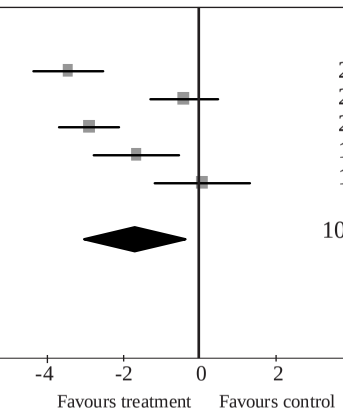

Figure 2. SLAV versus placebo for asthma symptoms.

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Review: Sublingual immunotherapy in children with respiratory allergy
Comparison: 03 Eye symptom scores
Outcome: 01 Eye symptom scores

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Year
Tari	30	7.30 (0.85)	28	9.50 (0.80)		49.30	-2.63 [-3.34, -1.91]	1990
Vourdas	34	0.20 (0.47)	32	0.56 (1.26)		50.70	-0.38 [-0.87, 0.11]	1998
	64		60			100.00	-1.49 [-3.69, 0.72]	

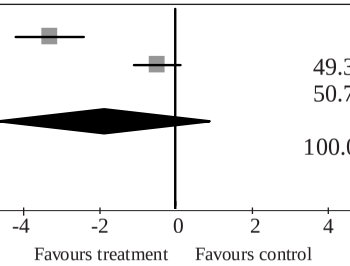

Figure 3. SLAV versus placebo for conjunctival symptoms.

Review: Sublingual immunotherapy in children with respiratory allergy
Comparison: 04 Medication scores
Outcome: 03 Medication scores

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Year
Vourdas	34	1.12 (2.27)	32	1.64 (3.01)		28.72	- 0.19 [- 0.68, 0.29)	1998
La Rosa	20	1.48 (2.04)	21	3.29 (3.73)		27.58	- 0.59 [- 1.21, 0.04]	1999
Pajno	12	82.68 (32.38)	12	205.20 (32.38)		19.97	- 3.65 [- 5.04, - 2.27]	2000
Bahceciler	8	1.25 (1.04)	7	1.57 (1.25)		23.74	- 0.26 [- 1.28, 0.76]	2001
	74		72			100.00	- 1.01 [- 2.06, 0.04]	

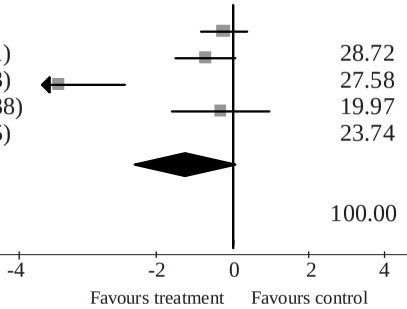

Figure 4. SLAV versus placebo for medication requirements.

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Sensitivity analysis

Significant heterogeneity was observed in the analysis of all symptom and medication requirement scores. As a sensitivity analysis we reanalyzed the data using a fixed effect model. SMD and 95% CI were:

- Nasal symptoms: -0.47 (-0.74, -0.20), p=0.0008.
- Bronchial symptoms: -1.60 (-1.93, -1.26) p< 0.00001.
- Ocular symptoms: -1.09 (-1.50, -0.69) p<0.00001.
- Medication requirements: -0.54 (-0.89, -0.19) p=0.002.

Secondary outcomes

Adverse effects

Safety was evaluated in all the studies [20-26]. Table 2 exhibits the adverse effects observed in the active and placebo groups. Of 129 children in the active group, 123 achieved the programmed maintenance dose and completed the study. Of the 6 remaining patients, 1 reduced the maintenance dose and continued the trial and 5 discontinued the study 1 due to local swelling and 4 because of gastrointestinal complaints. One of the 127 patients receiving placebo discontinued the study because of gastrointestinal complaints. No patient experienced anaphylaxis or other severe systemic adverse effects. One child, receiving placebo, had an asthma crisis that required hospitalization [22].

Skin reactivity to the allergen

A reduction in the degree of skin reactivity to the allergen was observed in 4 studies [20, 22, 25, 26]. In turn, Hirsch and cols. [21] observed no change in cutaneous reactivity.

Serum IgE levels

In none of the studies [20, 22, 25, 26] that measured them, were the IgE levels modified by SLAV.

Serum IgG levels

Two trials showed IgG levels increases by 6 [24] and by 2 [22] times their baseline values. IgG levels were not modified in the remaining 3 studies [21, 23, 25] that measured them.

Discussion

The characteristics of sublingual allergen vaccination: safe, without injections and home administered, determine that this route is contemplated as an attractive alternative to the injection one, especially for children with respiratory allergy. However, before such treatment can routinely be recommended, SLAV efficacy and safety should be proven. Whereas safety has been long confirmed from both clinical [13, 28] and post-marketing surveillance studies [8, 29], a degree of disparity regarding efficacy has been observed and, at least partially, attributed to inadequate trial designs [9]. In this aspect, a recent meta-analysis has confirmed the efficacy of SLAV in reducing symptoms and medication requirements of adult patients with allergic rhinitis secondary to both perennial and seasonal allergens [10]. However, according to the same study, such observation is not extrapolable to children [10], although these results have been recently questioned [30].

In the present report, we evaluated efficacy (symptom scores and drug intake) of sublingual allergen vaccination in paediatric population. We identified 16 clinical trials exclusively performed in children (≤14 years-old). Seven of them, enrolling 256 children (129 SLAV and 127 placebo receptors), complied with our quality criteria (proper allergen selection, randomized, placebo-controlled double-blind trials and adequate definition of end points), and they were selected for analysis. According to available data [31] SLAV tolerance was good, with mild oral immediate itching or mild gastrointestinal complaints as the most frequent side effects. Neither systemic nor severe adverse reactions were observed; only one asthma attack that required hospitalization and affecting to placebo recipient was reported [22].

To solve the problem derived from the different scales used by each author to measure the same variable, we used the standardized mean difference (SMD) that transforms all outcomes to the same scale. The SMD quantifies the number of standard deviations whose mean is modified by the treatment. In our case, the satisfactory effect for SLAV would be translated into a shift of SMD towards negative values albeit the findings were not always statistically significant. In keeping with that, we observed that in children SLAV reduced both symptom (asthma, rhinitis and conjunctivitis) scores and drug intake scores.

Evidence obtained from subcutaneous allergen vaccination (SCAV) points towards the existence of optimal doses of allergen [5, 32] that must be regularly administered during a period of time whose duration directly relates with the clinical efficacy of the treatment after its cessation [33]. Whereas in the subcutaneous route, the optimal allergen dose is conditioned by the onset of adverse effects; the safety of the sublingual route determines that high doses of allergen, up to 20 times those administered in SCAV, can be given without significant side effects, which handicaps the establishment of an optimal dose for SLAV. In keeping with it we observed a wide degree of variation of the doses of allergen administered in each study. It is noteworthy that the trial that administered SLAV for the

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shortest maintenance period (6 months) and also included the smallest number of patients (15 children; 8 active and 7 placebo) [20], was the only one in which neither asthma nor rhinitis improved, suggesting the need of administering SLAV for a minimum time and also, the convenience of analyzing larger samples of patients.

It is very likely that the significant heterogeneity observed between the results of the different studies is related to differences in the formulation of each clinical trial (dose of allergen, frequency, and maintenance period). Other factors that can contribute to heterogeneity such as the participants (paediatric population), the means of assessing the outcomes (clinical scores) or the methodological quality of the studies (all double-blind placebo-controlled) can be clearly excluded from our analysis. It is noteworthy that the values of the SMD obtained by the fixed effect model were quite similar to those of the random model, which confirms the validity of the results. The overall results from the fixed effect approach is an average measure of treatment effect; on the other hand, the random effect approach gives more weight to the results of smaller studies, in our case those of *Bahçeciler* et al. [20].

Changes in both *in vivo* (skin or target organ reactivity) and *in vitro* (serum immunoglobulin, inflammatory markers, T cell allergen specific responses) parameters have been commonly used to evaluate allergen vaccination efficacy, mainly when delivered by the subcutaneous route [31]. So, decreases in allergen specific IgE linked to rises in allergen specific IgG values are traditionally associated to the subcutaneous route [32]. However, these modifications seem not to be constant and reproducible in SLAV [31], consistently with our findings since even though one study reported increases in serum IgG levels by six times their baseline values, in 3 out of 5 trials IgG was not modified and all the studies failed to observe changes in IgE. In turn, most trials (4 out of 5) showed decreases in skin reactivity. It is remarkable that neither skin reactivity nor immunological changes were in our analysis primary outcomes and that some clinical trials [18, 19] were discarded because they offered no clinical information.

We conclude that SLAV is an effective and safe alternative to the subcutaneous route in the treatment of respiratory allergy in children, since it reduces symptoms and medication requirements. However, further randomized and properly designed trials are needed in order to elucidate a number of questions about the sublingual route such as the optimal conditions for its administration (dose of allergen, interval between doses, duration of the maintenance period), its ability to modify the natural history of allergic disease, its potency to control respiratory symptoms compared not with placebo but with subcutaneous allergen vaccination, the existence of clinical or immunological indices that allow to monitor and predict the response, and finally, whether results can also be extended to other allergens than house dust mite and some pollens.

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References

1. Moller, C., Dreborg, S., Ferdousi, H. A., Halken, S., Host, A., Jacobsen, L., . Koivikko, A., Koller, D. Y. Niggemann, B. Norberg, L. A., Urbanek, R., . Valovirta, E and Wahn, U. 2002. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 109(2):251-6.
2. Durham, S. R., Ying, S., Varney, V.A., Jacobson, M.R., Sudderick, R.M., Mackay, I.S., Kay, A.B. and Hamid, Q.A. 1996. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. J Allergy Clin Immunol 97(6):1356-65.
3. Tabar, A. I., Garcia, B.E., Rodriguez, A., Olaguibel, J.M., Muro, M.D and Quirce, S. 1993. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. Allergy 48(6):450-3.
4. Frew, A. J. 1993. Injection immunotherapy. British Society for Allergy and Clinical Immunology Working Party. Bmj 307(6909):919-23.
5. Bousquet, J., Lockey, R. and Malling, H. 1998. WHO Position Paper. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. Allergy 53(44):3-42.
6. Passalacqua, G., and Canonica, G. W. 1996. Alternative routes for allergen-specific immunotherapy. J Investig Allergol Clin Immunol 6(2):81-7.
7. Lopez, S., Pelaez, A., Navarro, L.A., Montesinos, E., Morales, C. and Carda, C. 1994. Aluminium allergy in patients hyposensitized with aluminium-precipitated antigen extracts. Contact Dermatitis 31(1):37-40.
8. Di Rienzo, V., Pagani, A., Parmiani, S., Passalacqua, G. and Canonica, G.W. 1999. Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients. Allergy 54(10):1110-3.
9. Malling, H. J. 2002. Is sublingual immunotherapy clinically effective? Curr Opin Allergy Clin Immunol 2(6):523-31.
10. Wilson, D. R., Torres, L.I. and Durham, S.R. 2003. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev(2):CD002893.
11. Alderson P, Green S, and Higgins JPT. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]. In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd, Alderson P, Green S, Higgins JPT, editors. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]. In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.
12. Almagro, E., Asensio, O., Bartolome, J.M., Bosque, M., de la Hoz, B., Dolz, I., Elorza, J., Ferreiro, M., Garcia, J.M., Losada, E. and et al. 1995. [Multicenter drug surveillance of sublingual immunotherapy in allergic patients]. Allergol Immunopathol (Madr) 23(4):153-9.
13. Andre, C., Vatrinet, C., Galvain, S., Carat, F. and Sicard, H. 2000. Safety of sublingual-swallow immunotherapy in children and adults. Int Arch Allergy Immunol 121(3):229-34.
14. Bernardis, P., Agnoletto, M., Puccinelli, P., Parmiani, S. and Pozzan, M. 1996. Injective versus sublingual immunotherapy

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in Alternaria tenuis allergic patients. J Investig Allergol Clin Immunol 6(1):55-62.
15. Di Rienzo, V., Puccinelli, P., Frati, F. and Parmiani, S. 1999. Grass pollen specific sublingual/swallow immunotherapy in children: open-controlled comparison among different treatment protocols. Allergol Immunopathol (Madr) 27(3):145-51.
16. Di Rienzo, V., Marcucci, F., Puccinelli, P., Parmiani, S., Frati, F., Sensi, L., Canonica, G.W. and Passalacqua, G. 2003. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy 33(2):206-10.
17. Mastrandrea, F., Serio, G., Minelli, M., Minardi, A., Scarcia, G., Coradduzza, G. and Parmiani, S. 2000. Specific sublingual immunotherapy in atopic dermatitis. Results of a 6-year follow-up of 35 consecutive patients. Allergol Immunopathol (Madr) 28(2):54-62.
18. Tari, M. G., Mancino, M., Madonna, F., Buzzoni, L. and Parmiani, S. 1994. Immunologic evaluation of 24 month course of sublingual immunotherapy. Allergol Immunopathol (Madr) 22(5):209-16.
19. Yuksel, H., Tanac, R., Gousseinov, A. and Demir, E. 1999. Sublingual immunotherapy and influence on urinary leukotrienes in seasonal pediatric allergy. J Investig Allergol Clin Immunol 9(5):305-13.
20. Bahceciler, N. N., Isik, U., Barlan, I.B. and Basaran, M.M. 2001. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol 32(1):49-55.
21. Hirsch, T., Sahn, M. and Leupold, W. 1997. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. Pediatr Allergy Immunol 8(1):21-7.
22. La Rosa, M., Ranno, C., Andre, C., Carat, F., Tosca, M.A. and Canonica, G.W. 1999. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 104(2 Pt 1):425-32.
23. Pajno, G. B., Morabito, L., Barberio, G. and Parmiani, S. 2000. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. Allergy 55(9):842-9.
24. Tari, M. G., Mancino, M. and Monti, G. 1990. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. Allergol Immunopathol (Madr) 18(5):277-84.
25. Vourdas, D., Syrigou, E., Potamianou, P., Carat, F., Batard, T., Andre, C. and P. S. Papageorgiou. 1998. 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 53(7):662-72.
26. Wuthrich, B., Bucher, C., Jorg, W., Bircher, A., Eng, P., Schneider, Y., Schnyder, F., Eigenmann, P., and Senti, G. 2003. Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. J Investig Allergol Clin Immunol 13(3):145-8.
27. Pajno, G. B., Vita, D., Parmiani, S., Caminiti, L., La Grutta, S. and Barberio, G. 2003. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. Clin Exp Allergy 33(12):1641-7.
28. Grosclaude, M., Bouillot, P., Alt, R., Leynadier, F., Scheinmann, P., Rufin, P., Basset, D., Fadel, R. and Andre, C. 2002. Safety of various dosage regimens during induction of sublingual immunotherapy. A preliminary study. Int Arch Allergy Immunol 129(3):248-53.
29. Lombardi, C., Gargioni, S., Melchiorre, A., Tiri, A., Falagiani, P., Canonica, G.W. and Passalacqua, G. 2001. Safety of sublingual immunotherapy with monomeric allergoid in adults: multicenter post-marketing surveillance study. Allergy 56(10):989-92.
30. Olaguibel, J. M. Misclasification of a clinical trial. Change of results. http://www.update-software.com/ccng/ccng.exe?
31. Canonica, G. W., and Passalacqua, G. 2003. Noninjection routes for immunotherapy. J Allergy Clin Immunol 111(3):437-48; quiz 449.
32. Olaguibel, J. M., Tabar, A.I., Garcia Figueroa, B.E. and Cortes, C. 1997. Immunotherapy with standardized extract of Dermatophagoides pteronyssinus in bronchial asthma: a dose-titration study. Allergy 52(2):168-78.
33. Des Roches, A., Paradis, L., Knani, J., Hejjaoui, A., Dhivert, H., Chanez, P., and Bousquet, J. 1996. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation. Allergy 51(6):430-3.

JM Olaguíbel, MD, PhD

Sección de Alergología. C.S. Conde Oliveto
Plaza de la Paz s/n
31003 Pamplona
Spain
Phone: 34 848 42 93 08
Fax: 34 848 42 92 71
e-mail: jmolaguibel@telefonica.net

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