

ORIGINAL ARTICLE

Sublingual immunotherapy in asthma and rhinoconjunctivitis; systematic review of paediatric literature

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Aims: To evaluate the clinical efficacy of sublingual immunotherapy (SLIT) in respiratory allergy in children.

Methods: A systematic literature review was conducted. The search was focused on all the double blind (and double dummy if necessary) studies. Search strategy: Medline, Embase, Cochrane Controlled Trial Register, Abstract of Cochrane Airways Group, hand search, and archives of some SLIT producers. All the selected studies were assessed and evaluated for quality in a standardised independent way.

Results: Eight randomised, double blind, placebo controlled studies on SLIT were selected. Five studies were run with house dust mite (HDM), one with olive pollen, one with wall pellitory (*Parietaria*) pollen, and one with grass pollen. A quantitative evaluation of the studies was not possible because the outcomes and the results of single studies were presented according to different criteria. Therefore only qualitative analysis was performed. No clinically relevant results were shown, independently from statistical significance, in the use of SLIT for respiratory allergies due to seasonal allergens (olive, wall pellitory, and grass pollens) and, on the whole, for rhinoconjunctivitis due to HDM in children. For mild to moderate persistent asthma due to HDM, statistically significant and low to moderate relevant clinical effects were observed.

Conclusions: SLIT can be currently considered to have low to moderate clinical efficacy in children of at least 4 years of age, monosensitised to HDM, and suffering from mild to moderate persistent asthma. This benefit seems to be adjunctive with respect to the environmental preventive measures against HDM.

Recently specific immunotherapy (SIT) by the sublingual route (sublingual immunotherapy, SLIT) has been increasing in acceptance in clinical practice, mainly in Central Europe;¹ it is currently the most used form of specific immunotherapy in children. This is due to its ease of administration and documented safety.^{2,3} However, there are still doubts in the scientific community about its clinical efficacy.^{4–8}

Clinical efficacy of SIT in allergies has been analysed in two systematic reviews, one of which was based only on injected SIT.⁹ The authors of the second systematic review¹⁰ only analysed the efficacy of SLIT in allergic rhinitis. They found that SLIT is a safe treatment which significantly reduces symptoms and medication requirements in allergic rhinitis in the adult population; but these results could not be confirmed in the paediatric group. In this review, however, one apparently eligible study¹¹ was not included, and the results of another,¹² which was conducted among children, were inexplicably included in the adult population. We therefore decided to perform a new systematic review on the efficacy of SLIT in allergic asthma and rhinoconjunctivitis in children. We posed the following questions:

- Is SLIT effective in reducing symptoms of allergic asthma and/or rhinoconjunctivitis in children?
- Is SLIT capable of reducing the need for rescue and preventive drugs for asthma and/or rhinoconjunctivitis in children?

METHODS

Objectives of the systematic review

- To identify all randomised and double blind (and double dummy if necessary) clinical studies on clinical efficacy of SLIT administered according to the swallow or the spit technique in children (aged 0–18 years) suffering

from asthma and/or rhinoconjunctivitis due to inhalant allergens.

- To evaluate the methodological quality of the identified studies.
- To estimate the overall efficacy of SLIT on symptoms of asthma and/or rhinoconjunctivitis and on consumption of rescue or preventive drugs from both a qualitative and (if possible) a quantitative point of view.

Search of the literature

We used the following instruments for the search of the relevant studies:

- The Pubmed search engine to enter the Medline database (search extended to June 2003) using the terms: asthma, wheezing, conjunctivitis, rhin*, hay fever, immunotherapy, desensitisation, hyposensitisation, allergen immunotherapy, sublingual, oral, local.
- The Embase database (search extended to June 2003) using the above terms plus perennial rhinitis, systemic desensitisation, papillary conjunctivitis, school child and pre-school child, oral/sublingual drug administration.

We extended our search for relevant studies looking through or by means of:

- The Cochrane Controlled Trials Register.
- Abstracts of the Cochrane Airways Group.
- References of some reviews published on the subject.^{4–8}
- References of the clinical studies identified as relevant.

Abbreviations: HDM, house dust mite; SIT, specific immunotherapy; SLIT, sublingual immunotherapy

Table 1 Demographic and allergic characteristics of included studies

Study	No. of patients	Age of patients	Country	Asthma	Rhinitis	Conjunctivitis	Allergy	Duration of treatment	SLIT	Manufacturer	Cumulative dose of major allergen
Tari <i>et al</i> (1990)	66 pt 21 F/37 M*	5–12 y	Italy	Yes	Yes	Yes	D.pt/D.f.	18 mth	Drops	Neo Abello	75000 STU, Der p 1
Hirsch <i>et al</i> (1990)	30 pt 10 F/20 M	6–15 y	Germany	Yes	Yes	No	D.pt.	12 mth	Drops	Allergopharma	570 µg, Der p 1
Pajno <i>et al</i> (2000)	24 pt 11 F/13 M	8–15 y	Italy	Yes	No	No	D.pt.	24 mth	Drops	ALK-Abello	244 µg, Der p 1
Ippoliti <i>et al</i> (2003)	86 pt 50 F/36 M	5–12 y	Italy	Yes	Yes	Yes	D.pt	6 mth	Drops	ALK-Abello	60 µg, Der p 1
Bahçeciler <i>et al</i> (2001)	15 pt 7 F/8 M	7–18 y	Turkey	Yes	Yes	No	D. pt/D.f.	6 mth	Drops	Stallergenes	560 µg, Der p 1
Vourdas <i>et al</i> (1998)	66 pt 17 F/49 M	7–17 y	Greece	Yes	Yes	Yes	Olive	24 mth	Drops	Stallergenes	8100 µg, Ole e 1
La Rosa <i>et al</i> (1999)	41 pt 16 F/25 M	6–14 y	Italy	Yes	Yes	Yes	Parietaria i.	24 mth	Drops	Stallergenes	52100 µg, Par J 1
Caffarelli <i>et al</i> (2000)	44 pt 19 F/25 M	4–14 y	Italy	Yes	Yes	Yes	Grass	9 wk**	Tablets	Lofarma	37250 AU, mix

A, active treatment; P, placebo; F, female; M, male; D. pt., *Dermatophagoides pteronyssinus*; D.f., *Dermatophagoides farinae*; Pariet. i., *Parietaria judaica*; S-swallow, sublingual swallow; S-spit, sublingual spit; Der p 1, the *Dermatophagoides pteronyssinus* major allergen; Ole e 1, the olive pollen major allergen; Par J 1, the wall pellicular (*Parietaria*) pollen major allergen; mix, the standard mixed grass pollen allergens.
*The authors report the ratio F/M only for patients who completed the follow up, i.e. 58.
**In this study the treatment lasted 9 weeks and the follow up 2 months. In other studies the duration of treatment and follow up is the same.

- Hand searching of the last two year' indexes of: *Allergy, Annals of Allergy, Asthma and Immunology, Clinical and Experimental Allergy, Pediatric Allergy and Immunology, The Journal of Allergy and Clinical Immunology, Archives of Disease in Childhood, Pediatrics, and The Journal of Pediatrics.*
- The archives of some SLIT producers (ALK-Abellò, Anallergo, Bracco, Lofarma, Stallergenes).

As first screening, only abstracts were reviewed; if insufficient, the analysis was extended to the full text.

Selection of studies and quality assessment
Inclusion criteria

Eligible studies had to fulfil as a first step the following points:

- Be based only on commercial extracts of inhalant allergens (HDM, pollens, pets' epithelia, moulds) administered through the sublingual route (swallow or spit).
- Include patients with respiratory symptoms (asthma, rhinitis, rhinoconjunctivitis).
- Include only children (age range 0–18 years) or, in the case of a mixed paediatric/adult population, the results for the paediatric subjects could be extracted.
- Be based on clinical evaluations (symptom and drug scores).
- Be published in full text.
- Be randomised and run according to a double blind (and double dummy if necessary) design.
- The control group was treated with placebo, SIT administered by routes other than the sublingual one, or drugs.

Exclusion criteria

Studies were excluded if the drop out during follow up was equal or more than 20% of randomised patients.¹³

Definition of the outcomes

At least one of the following clinical outcomes had to have been studied:

- Asthma and/or rhinoconjunctivitis symptoms (assessed by means of a scoring system).
- Intake of rescue and preventive drugs (assessed by means of a scoring system).

A majority of the four reviewers decided the inclusion of each study in this review, after an independent evaluation.

Methodological quality of the included studies

The methodological quality of the included studies was evaluated according to the criteria given by the Evidence-Based Medicine Working Group.¹³ For every paper the following were analysed: the randomisation process; the efficacy of randomisation (through analysis of the "classical" table 1 of any RCT, where authors usually compare sex, economic status, age, and other specific characteristics); sample size calculation; clear definition of end points; drop outs—those lost during follow up; compliance; intention to treat analysis; placebo concealment; and run in. See table 2 for specific details on each paper. Overall the methodological quality of the studies was not very good. For example, only one¹⁵ had a priori sample size calculation, and only three studies out of eight clearly stated the methodology of randomisation. On the other hand, all the primary end points were well defined and were decided a priori, such as the plan for statistical analysis.

Table 2 Methodological characteristics of included studies

Study	Randomisation process	Assessment of efficacy of randomisation†	Sample size calculation	Clear definition of end points	Drop out or lost during follow up	Compliance	Intention to treat analysis	Placebo concealment	Run in
Tari <i>et al</i> (1990)	NR	No	No	Yes	8/66 (12%)	NR	Yes	Yes	No
Hirsh <i>et al</i> (1990)	Code provided by manufacturer	Yes	Yes	Yes	None	83%	Yes	Yes	Yes
Pajno <i>et al</i> (2000)	Keyed code	Yes	No	Yes	3/24 (12.5%)	NR	Yes	Yes	Yes
Bahçeciler <i>et al</i> (2001)	NR	Yes	No	Yes	None	NR	Yes	Yes	Yes
Ippoliti <i>et al</i> (2003)	NR	Yes	No	Yes	None*	Good*	Yes*	Yes	Yes
Vourdas <i>et al</i> (1998)	NR	Yes	No	Yes	2/66 (3%)	NR	No	Yes	No
La Rosa <i>et al</i> (1999)	NR	Yes	No	Yes	8/41 (19.5%)	98%	No	Yes	No
Caffarelli <i>et al</i> (2000)	PC generated list	Yes	No	Yes	4/44 (8.4%)	“Very good”	Yes	Yes	No

NR, not reported.

†Dates derived by “classical” table 1 of respective papers where demographic and other specific items are usually compared in both groups.

*This information was given directly by the authors.

RESULTS

A total of 505 papers were examined. One paper could not be found as full text and was therefore excluded.¹⁴ However, no review or original study subsequently published on this subject has ever mentioned this paper. No study was excluded because of the drop out during follow up being $\geq 20\%$ of randomised patients. In order not to lose any papers the bibliographic research was conducted without any specific limit; all 505 papers described criteria of selection and inclusion. Eight papers^{11, 12, 15–20} fulfilled the selection and inclusion criteria. In all of them the comparison was made against placebo. No studies comparing SLIT to immunotherapy administered by other routes or to drugs were found in children. Further details of the search strategies and excluded papers can be obtained from the authors on request.

Tables 1–3 summarise demographic, allergic, and methodological characteristics of the included studies.

Description of the results of each clinical study

Studies on HDM allergy

*Tari et al, 1990*¹²

In the active group the weekly score significantly decreased from 10 to 6 for asthmatic symptoms (equivalent to 40%) and from 14 to 8 for rhinitis symptoms (equivalent to 43%). No significant improvement of the conjunctival symptoms score was detected. No significant improvement in the placebo group was observed for any of the above parameters. On average, the percentage of patients in the active group

experiencing a reduction of at least 20% of the intake of drugs was 40% higher than in the placebo group.

*Hirsch et al, 1997*¹⁵

The daily score for asthmatic symptoms showed a significant reduction in the active treated patients; the relative improvement at the end of the study seems remarkable (80%), but the difference in absolute value was only -0.29 points/day. No significant improvement in the placebo group was observed and the difference between the groups was significant at the end of the study. No differences were registered between groups in clinical improvement based on the subjective assessment, or in drug consumption. The score of rhinitis symptoms did not differ significantly either within or between groups.

*Pajno et al, 2000*¹⁸

In the active group the monthly score for nocturnal asthmatic symptoms significantly decreased by 57.1%, going from an average score of 14 to 6. No significant improvement in the placebo group was observed. At the end of the treatment, the difference between placebo group score (13.2) and active group score (6) was significant. The monthly number of asthma episodes significantly decreased from 1.73 to 0.68 (that is, -60.7% , in the active group), and from 1.6 to 1.3 (that is, -18.7% , in the placebo group). At the end of the treatment, the difference between placebo group and active group was significant. In the active group the annual drug

Table 3 Other methodological characteristics of included studies

Citation	Environmental preventive measure against mites	Mono multi-sensitisation	Clear definition of asthma/rhinitis/conjunctivitis	Clear definition of scoring system for symptoms	Clear definition of scoring system for drug use
Tari <i>et al</i> (1990)	Yes	NR	No	Yes	No
Hirsh <i>et al</i> (1990)	Yes	Multi	Yes	Yes	No
Pajno <i>et al</i> (2000)	Yes	Mono	Yes	Yes	Yes
Bahçeciler <i>et al</i> (2001)	Yes	Mono	Yes	Yes	Yes
Ippoliti <i>et al</i> (2003)	NR	Mono	Yes	Yes	Yes
Vourdas <i>et al</i> (1998)	–	Multi	Yes	Yes	Yes
La Rosa <i>et al</i> (1999)	–	Mono	No	Yes	Yes
Caffarelli <i>et al</i> (2000)	–	Mono	No	Yes	Yes

score significantly changed from 259.68 to 82.68, with a -68.2% reduction significantly higher than in the placebo group (-30.2%). The four month average score of the patient's subjective assessment significantly changed only in the active group, from 5.1 to 2.5, with a 49% improvement.

*Bahçeciler et al, 2001*¹⁹

In the active group the daily score for asthmatic symptoms significantly decreased from 0.64 to 0.30, with a 53% relative reduction. There was also a significant reduction from 0.17 to 0.03 of the score for β_2 agonists but no difference in the use of inhaled steroids and in patients' subjective assessment of the clinical outcome. More clinically relevant, the number of acute asthma episodes at the end of the treatment period was 3 in the active group compared to 30 in the placebo group. Differences within the active group of the score for rhinitis symptoms and subjective assessment were not significant, whereas the use of nasal steroids was statistically significant (daily average score changed from 3 to 1). No significant difference for any of the above parameters was observed in the placebo group. Finally, there was no statically significant difference between the two groups in the analysis of the daily asthma and rhinitis scores at the end of the study.

*Ippoliti et al, 2003*²⁰

In the active group there was a significant, and clinically relevant, decrease in asthma scores from 3.28 (daily mean of run-in period) at baseline to 1.28 (daily mean of six months of therapy) with a 61% relative reduction. Daily rhinitis score significantly decreased (from 0.84 to 0.39) with a 54% relative reduction, and FEV₁ significantly improved (from 83.4% to 92.6%). No significant difference for any of the above parameters was observed in the placebo group.

Studies on other allergens

*Vourdas et al, 1998*¹⁶

In this trial the outcomes were reported as daily mean symptom scores at the peak of the pollen season in both years investigated. The differences between the scores of asthmatic symptoms at the peak of the first (active = 0.15, placebo = 0.3) and the second pollen season (active = 0.04, placebo = 0.28) were significant. A significant difference was observed for conjunctival symptom scores (active = 0.03, placebo = 0.22) only at the pollen peak during the second year. No significant difference was reported for rhinitis symptom scores. No difference in drug consumption or subjective assessment for the same period was detected.

*La Rosa et al, 1999*¹⁷

No significant difference was reported between the active and the placebo group with reference to the score of rhinitis symptoms during the observation period. There was a significant difference in the active group compared to placebo in the proportion of patients with a clinical improvement of at least 30% in rhinitis symptoms (87.5% v 47.5%). A significant difference in active group compared to placebo was also observed for the daily score of drugs for rhinitis, but only during the first week of the first pollen season (0.38 v 0.95).

*Caffarelli et al, 2000*¹¹

A significant difference for the weekly score for asthmatic symptoms between the active (2.7) and the placebo group (4.6) was reported. This difference corresponds to a saving of 0.27 points/day for the active group. However, no significant saving of drugs was reported. No differences were seen in the weekly score for rhinitis and conjunctivitis symptoms.

DISCUSSION

The increase of both the debate and the number of clinical studies on SLIT led us to perform a systematic review on the efficacy of this form of immunotherapy in children.

The immunological aspects of SLIT are not still clear, especially in comparison with injection specific immunotherapy.²¹⁻²⁴ Many studies on SLIT have focused on possible decrease of serum IgE or/and increase of IgG1 and IgG4, but these changes were not constant and reproducible.²⁵ Recently SLIT has been proved to reduce intercellular adhesion molecule 1 expression on nasal epithelial cells and to decrease methacholine responsiveness.²⁸

The ARIA document⁶ supports the use of SLIT in seasonal allergic rhinitis in children. We cannot agree, as of three studies mentioned in this document to support its use in this indication, only one¹⁶ dealt with children showing no significant differences for rhinitis symptoms, whereas the other two^{29, 30} investigated a mixed population (adults and children), but the outcomes regarding the paediatric sample cannot be extrapolated.

Moreover, in the studies we reviewed, the number of patients with a single allergen is low, the overall efficacy is clinically irrelevant, and the methodological validity is poor. According to our results the judgement on the efficacy of SLIT in seasonal respiratory allergies in children should wait until proper studies are available.

Regarding the clinical efficacy of SLIT in asthma due to HDM, in all five studies we reviewed, the improvement of the before and after asthmatic score was statistically significant only in the active group; in three^{12, 18, 20} it was also clinically relevant. No relation among relevance of clinical results, duration of treatment, and/or degree cumulative dose, was observed. Four of five studies performed environmental preventive measures against HDM; the observed efficacy of SLIT seems to be additional to these preventive measures.

With reference to rhinitis due to HDM, the studies we reviewed showed a significant and clinically relevant effect in two cases^{12, 20} and no effects in the other two.^{15, 19} For rhinoconjunctivitis due to HDM, the judgement is not clear and still pending on new data. It is difficult to understand why, in children, SLIT improves asthmatic symptoms, while this benefit is not so clearly evident for rhinitis.

In conclusion, the use of SLIT can be recommended in children of at least 4 years of age suffering from mild to moderate persistent asthma due to monosensitisation to HDM or having further sensitisation without clinical relevance. The efficacy on symptoms and on drug consumption can be defined as low to moderate and probably considered additive to the efficacy achievable with the environmental avoidance measures.

However, the following need to be explored: a comparison of SLIT with pharmacological prevention, an economic cost-benefit analysis, optimal dose standardisation and duration of treatment, the prevention of new sensitisation, and the real improvement of quality of life of allergic children.

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IMAGES IN PAEDIATRICS.....

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Bovine insulin therapy and lipohypertrophy



An 8 year old boy with a two year history of type 1 diabetes mellitus, treated with purified bovine insulin, developed lipohypertrophy at the site of insulin injection (see fig). Lipohypertrophy is a relatively more common complication than lipatrophy with purified insulin treatment. It should be specifically looked for before increasing insulin dose whenever a previously euglycaemic patient presents with uncontrolled blood glucose. Good glycaemic control can be achieved by just rotating the injection site in the uninvolved area. The lipohypertrophy is linked to the local lipogenic action of insulin and is more likely related to the frequency of injections at a given site and purity of insulin than to the dose or species of insulin.

When purified insulin preparations were not available, lipatrophy at the injection site was relatively common, and was attributed to the impurities in the preparation, leading to immune complex deposition and subsequent atrophy.

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