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 performed 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.

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.
- References of the clinical studies identified as relevant.

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

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. 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 one 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.
RESULTS

A total of 505 papers were examined. One paper could not be found as full text and was therefore excluded. 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 ≥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 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

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

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

In the active group the monthly score for nocturnal asthmatic episodes 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
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.

Bahc€eciler et al, 2001
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 $\beta_2$ 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
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
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, pla-

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The immunological aspects of SLIT are not still clear, 
especially in comparison with injection specific immuno-
therapy.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.26

The ARIA document 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 one14 dealt with children showing no 
significant differences for rhinitis symptoms, whereas the 
other two26 27 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 signifi-
cant only in the active group; in three12 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 environ-
mental 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 cases12 16 and no effects in the other two.13 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 rele-
vance. 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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REFERENCES

IMAGES IN PAEDIATRICS

Bovine insulin therapy and lipohypertrophy

A 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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www.archdischild.com
Bovine insulin therapy and lipo hypertrophy

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