

SUBLINGUAL IMMUNOTHERAPY IN CHILDREN WITH ALLERGIC RHINITIS

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ABSTRACT

This review aims to assess the role of sublingual immunotherapy (SLIT) for the treatment of allergic rhinitis in the paediatric population.

INTRODUCTION

The prevalence of allergic disease has been increasing over time and now represents a global health problem.¹ For example, allergic disease in the UK affects up to 40% of children² with allergic rhinitis accounting for a significant component of the allergic burden. There is also specific evidence for increasing prevalence of allergic rhinitis in the UK paediatric population,³ particularly among young children: data from Phase 3 of the ISAAC cross-sectional survey reveal 10.1% of UK children aged 6-7 and 15.3% of those aged 13-14 years reported symptoms of allergic rhino-conjunctivitis in the past 12 months.

Rhinitis has a number of different causes in children. In contrast to the case in adults, who frequently suffer from intrinsic rhinitis, the most common cause in children is that of allergic rhinitis (previously referred to as extrinsic rhinitis).⁴ Allergic rhinitis is an inflammatory condition of the nasal mucosa, characterised by anterior nasal symptoms of pruritus, sneeze, discharge and 'stiffness', which is induced by an IgE-mediated response.⁵ Allergic rhinitis can be classified according to the ARIA guidelines⁶ which differentiate between cases on the basis of symptom duration (intermittent or persistent) and severity (mild or moderate severe).

Sublingual immunotherapy (SLIT) has been proposed as a treatment for allergic rhinitis. SLIT induces immunological tolerance to the allergens which cause the immune-mediated inflammatory response that is characteristic of allergic rhinitis. It is therefore only appropriate for allergen-specific, immune-mediated causes of rhinitis. The precise mechanisms underlying the induction of immune tolerance by SLIT remain unclear.⁷ One possible mechanism is the production of blocking antibodies such as IgG4, which may suppress the cascade of allergic inflammation that results from recognition of antigen by IgE. In subcutaneous immunotherapy (SCIT), a rise in such blocking antibodies has been demonstrated over a 70-day course of house-dust mite (HDM) immunotherapy, while specific IgE did not change.⁸ However, not all studies could demonstrate this change.⁹ Another possibility is the induction of tolerance through the stimulation of T reg-

ulatory cells, although there is a lack of firm evidence to support this.⁷

Before any new treatment is recommended for allergic rhinitis, a number of factors must be considered as part of a risk/benefit analysis. The effect of the disease on the individual child needs to justify the treatment, which needs to have a proven track record of both safety and efficacy. The treatment also needs to be acceptable to the individual patient (and their parents), and the cost burden on the health system needs to be justifiable. This latter point is particularly relevant in the case of immunotherapy as the cost benefit ratios may not be immediately apparent, especially given the treatment's possible role in preventing future morbidity. These issues will be considered in turn.

QUALITY OF LIFE IN CHILDREN WITH ALLERGIC RHINITIS

Although symptoms of allergic rhinitis are not life-threatening they can have detrimental effects on the physical, psychological and social aspects of patient's lives. That allergic rhinitis can significantly decrease quality of life¹⁰ is often under-recognised by physicians and non-sufferers alike. Allergic rhinitis can have substantially negative impact on children.¹¹ Juniper and colleagues have developed validated 'Quality of Life Questionnaires' specific to allergic rhinitis in both adolescents (12-17 years)¹² and children (6-12 years).¹³ Adolescents were found to suffer similar effects on quality of life to adults although the effects on concentration, such as with schoolwork, were a particular problem. Younger children report particular problems with practical issues such as carrying tissues or taking medication.

Symptoms of rhinitis and the associated underlying inflammation may cause lethargy, while nocturnal symptoms such as itch and congestion can affect the quality of sleep.¹⁴ Together, there are significant effects on a child's ability to perform well at school.¹⁵ Even uncomplicated seasonal allergic rhinitis may be associated with reduced ability to learn. This is a particular concern given that the timing of public examinations may coincide with the grass pollen season. A study comparing adolescents' examination performance during 'mock' examinations (conducted in winter) with formal examinations in spring/summer revealed that having current symptomatic hay fever was associated with a remarkable 50% increase in the risk of dropping an exam grade between winter and summer. For those taking hay fever medications and for those taking sedating medications the risk increases were 40% and 70% respectively.¹⁶

Learning problems may increase in severe perennial rhinitis or in rhinitis associated with complications such as sinusitis or eustachian tube dysfunction and conductive hearing loss.¹⁵ Unfortunately, treatment of allergic rhinitis with first-generation antihistamines may result in a further sedating effect.¹⁷ It is not uncommon for the older-generation sedating antihistamines to be used for the treatment of rhinitis as these medications are easily accessed, affordable and licensed for use in younger children. However, effective treatment of the

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underlying inflammation can help reduce this sleep disturbance¹⁸ and its resulting impact on education can therefore be used as justification on both medical and economic grounds.

SAFETY

The practice of administering gradually increasing doses of allergen extract in order to reduce the symptoms associated with subsequent exposure has a history dating back to 1911.¹⁹ The practice of SCIT became increasingly widespread over the course of the twentieth century, albeit not without problems. Twenty-six deaths were recorded in the UK between 1957 and 1986²⁰ and 46 deaths in the USA between 1959 and 1984.²¹ These deaths were due to anaphylaxis and bronchospasm. As a result, the practice of immunotherapy declined in the UK, while continuing to grow elsewhere. Most of the deaths that occurred were the result of incorrect dose administration, failure to recognise and treat reactions, lack of resuscitation equipment and the inclusion of patients with unstable asthma.²²

More recent work has supported the safety on SCIT²³ when conducted under standardised protocols²⁴ with systemic reactions complicating only 0.37% of injections and most such reactions involving urticaria alone.²⁵ If SLIT is to be considered a viable alternative to SCIT, there need to be clear data that it is at the very least comparably safe in children.

Andre *et al.*²⁶ reviewed the safety data from 8 double-blind placebo-controlled trials of the use of SLIT for a range of pollens and dust mites. This included a total of 472 adults and 218 children of whom a total of 347 received active treatment. No serious adverse events were reported; 145 adverse events were reported among the active group compared to 79 in the placebo group, with the most common being localised buccal symptoms. The rate of adverse events was no different between adults and children.

Di Rienzo, *et al.*²⁷ carried out postmarketing surveillance studies in children aged 2-15 years and then a later study focusing on children aged under 5. The first study included 268 children who received a total of over 96 000 doses of extract (including pollen, mould, cat and dust mite allergens) over periods ranging from 3 months to 7 years (average 34 months). Almost 25% of patients had coexistent asthma. Eight adverse reactions were reported (in 3% of patients). All the reactions were mild and only one required the use of an oral antihistamine. The later study²⁸ involved 126 children aged 3-5 years and included 390 000 doses of extract. Minor side-effects were reported by 5.6% of patients; again all were mild (oral itching, abdominal pain) and were controlled by dose adjustment. No difference was noted in the different allergens used. Indeed, even using higher doses of SLIT (300IR) in children under 5²⁹ failed to elicit any reactions severe enough to abandon treatment. Only one study³⁰ has reported more significant side-effects of asthma, urticaria and abdominal pain but no anaphylaxis. It can therefore be considered that SLIT is safe for use in children.

EFFICACY

A considerable body of work has confirmed the efficacy of subcutaneous immunotherapy³¹⁻³⁵ including its long-term efficacy after treatment has been discontinued.³¹⁻³⁴ There are increasing data relating to the efficacy of SLIT, which is now widely considered efficacious in adults. A systematic review and meta-analysis³⁶ of 22 trials involving 979 patients revealed that

SLIT significantly reduced both symptoms and medication scores when compared to placebo. This meta-analysis failed to find a significant clinical effect in children but recognised that the numbers were small given the lack of paediatric studies. A more recently published meta-analysis examined efficacy data relating exclusively to children. Penagos *et al.*³⁷ found 10 randomised, double-blind, placebo-controlled trials of SLIT in the treatment of children with allergic rhinitis where study outcome measures included the objective measurement of symptom scores and rescue medication use. A total of 245 children received SLIT and 239 received placebo. SLIT was found to be effective for the treatment of pollen-sensitised children but only for treatment durations of 18 months or longer. There was insufficient evidence for efficacy in children with symptoms related to HDM sensitisation although this was due to lack of sufficient studies. One study did not find overall benefit of SLIT in children with grass pollen allergy³⁸ although a subgroup analysis revealed an effect after 3 years of therapy for those children with more severe symptoms at enrolment. A more recent study has demonstrated long-term efficacy of SLIT.³⁹ Sixty children with allergic asthma/rhinitis and HDM sensitivity were randomised to either drug treatment alone or SLIT. The SLIT group showed significant improvement compared to controls not only at the end of the SLIT therapy but also at 4-5 years after discontinuation.

Immunotherapy may have benefits beyond simple symptomatic relief from AR. It is known that children with AR are likely to develop asthma⁴⁰ and it has been demonstrated that nasal allergen provocation in patients with AR results in generalised airway inflammation through upregulation of adhesion molecules.⁴¹ The possibility of interrupting this step in the allergic march from allergic rhinitis to asthma in early childhood considerably enhances the value of immunotherapy. Indeed, subcutaneous immunotherapy has been shown to have a role in the prevention of asthma in children with seasonal AR.⁴⁰ There are emerging data to indicate that SLIT may also have this potential.⁴² Novembre *et al.*⁴³ recruited 113 children aged 5-13 years with seasonal allergic rhinitis due to grass pollen allergy. None of the children started the study with significant seasonal asthma. Children received either SLIT for 3 years or standard drug treatment. Development of asthma was 3.8 times more frequent in the control group compared to those children who received SLIT. Other work has suggested that SCIT in children may prevent the development of further sensitisations to other allergens⁴⁴ while in adults, SCIT to birch pollen has been shown to decrease allergy to cross-reactive foods.⁴⁵ Larger studies are required to more definitely demonstrate these apparent immunomodulatory roles.

ACCEPTABILITY

SLIT would appear to offer some important advantages over SCIT for children including the lack of injections and reduced need for clinic visits (Table I). However, the move towards patient self-administration does raise the issue of compliance. Compliance is key to the efficacy of immunotherapy⁴⁶ and lack of compliance appears to be associated with increased side-effects. In the meta-analysis of paediatric studies, Andre *et al.*²⁶ found most discontinuations of treatment were the result of repeated, albeit minor, side-effects. In studies where side-effects did not lead to withdrawal, there appeared to be a tendency for parents to stop treatments when symptoms were relieved, in the belief that treatment was thus no longer required.⁴³ One study⁴⁷ compared compliance of SLIT to that of SCIT,

Table 1. Comparison of subcutaneous (SCIT) and sublingual immunotherapy (SLIT)

Consideration	SCIT	SLIT
Route of administration	Subcutaneous injection	Oral drops/tablet
Clinical monitoring	Administration under medical supervision ²⁴	Self-administered
Dosing regimen	Weekly or monthly intervals (after up dosing)	Daily or 3 times per week
Safety	Risk of severe reaction ^{20,21,25}	Risk of minor reaction ²⁶
Efficacy	Proven ³¹⁻³⁵	Proven ³⁶
Long-term efficacy	Proven ³¹⁻³⁴	Documented ³⁹
Prevention of asthma	Documented ⁴⁰	Documented ⁴³
Compliance	Good ⁴⁷	Variable ⁴⁷
Prevent development of new sensitisations	Documented ⁴⁴	No data available
Moderate allergic responses to cross reactive food allergens (OAS)	Documented ⁴⁵	No data available

(Adapted from 'Fight the Cause', ALK Abello, UK)

predictably finding that significantly greater numbers discontinued SLIT (21.5% compared to 10.9%, $p < 0.0005$). Interestingly, the most common reason for stopping treatment in both modalities was the cost of the treatment.

It is therefore clear that when self-administration is to be relied on, it is of particular importance that there is clarity regarding the parents' understanding of the treatment and their motivations. It is therefore relevant to consider parental educational and economic status before commencing treatment.⁴⁷

COST

While the high cost of allergic rhinitis to the economy has been demonstrated, in terms of lost productivity,⁴⁸ the cost of any new treatment needs to be carefully considered in the context of both public- and private-funded health care systems. The potential benefits of SLIT need to be balanced with its cost, with specific reference to the cost of current alternative options. The impact on quality of life and effect on learning in children increases with more severe symptoms.¹⁰ A child with moderate-severe allergic rhinitis during the grass pollen season may be managed with a daily non-sedating antihistamine, steroid nasal spray and daily oral leukotriene receptor antagonist.⁴⁹ Based on current UK drug costs for a 5-month course, this would result in an annual cost of £202.80 (UK prices based on Neoclaritin, Nasonex and Singulair) (Source: British National Formulary 2006). This compares to the current cost of sublingual grass pollen immunotherapy (Stallergens Staloral Grass pollen mix) of £180 per season. As a minimum 3-year course would be recommended, the overall cost of SLIT would be £1 075. This approximates to 5 years of maximal medical therapy mentioned above. If the efficacy of SLIT extends beyond this period, as expected, then the pharmaceutical cost savings would increase over time. This crude analysis does not take into account the potential savings from decreased doctor visits and, if asthma is prevented, the larger financial burden this could avoid. The particular value of sublingual over subcutaneous immunotherapy is the minimal number of doctor visits required to administer the therapy. Whether this cost would be offset by a difference in long-term efficacy or breakthrough symptoms requiring pharmacological management will become more apparent over time.

CONCLUSION

In conclusion, sublingual immunotherapy appears to be safe, efficacious and acceptable in the treatment of children with allergic rhinitis. The significant effects of more severe allergic rhinitis on a child's ability to learn and quality of life, coupled with apparent increased efficacy in severe cases and the cost of alternative medication, would justify the use of SLIT in this scenario. It is more difficult to justify in children with milder symptoms, who require less medication and suffer from fewer ill effects. However, if early evidence that SLIT may prevent the development of further sensitisations and later asthma is borne out, then there may be grounds to extend the indications for its use. Despite this, the issues around compliance in a self-administered medication still require patient selection to be carefully considered.

Declaration of conflict of interest

The authors declare no conflict of interest.

REFERENCES

- Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax* 2007; **62**: 91-96.
- Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004; **34**: 520-526.
- Asher MI, Montefort S, Bjorksten B, et al. ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**: 733-743.
- Gentile D, et al. Allergic rhinitis. In: Leung D, Sampson H, Geha R, Szefer S, eds. *Pediatric Allergy - Principles and Practice*. St Louis: Mosby, 2003: 287-297.
- Howarth PH. Disease pathogenic mechanisms in allergy: A rational basis for treatment. *BMJ* 1998; **316**: 757-761.
- Bachert C, van Cauwenberge P. The WHO ARIA (allergic rhinitis and its impact on asthma) initiative. *Chem Immunol Allergy* 2003; **82**: 119-126.
- Akdis CA, Barlan IB, Bahceciler N, Akdis M. Immunological mechanisms of sublingual immunotherapy. *Allergy* 2006; **61**: Suppl 81, 11-14.
- Jutel M, Akdis M, Budak F, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003; **33**: 1205-1214.
- Pajno GB, Morabito L, Barberio G, Parmiani S. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebocontrolled study. *Allergy* 2000; **55**: 842-849.
- Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. *Ann Allergy Asthma Immunol* 2000; **85**: 338-347.
- Blais MS. Allergic Rhinitis in Schoolchildren Consensus Group. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Curr Med Res Opin* 2004; **20**: 1937-1952.
- Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol* 1994; **93**: 413-423.
- Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. *J Allergy Clin Immunol* 1998; **101**(2 Pt 1): 163-70.
- Woods L, Craig TJ. The importance of rhinitis on sleep, daytime somnolence, productivity and fatigue. *Curr Opin Pulm Med* 2006; **12**: 390-396.
- Simons FE. Learning impairment and allergic rhinitis. *Allergy Asthma Proc* 1996; **17**: 185-189.
- Walker S, et al. Hayfever has a significant detrimental impact on national exam performance in UK teenagers: case control study. Unpublished data presented at BSACI Annual meeting, 2006.
- Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993; **71**: 121-126.

18. Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol* 1998; **101**: 633-637.
19. Noon L. Prophylactic inoculation against hayfever. *Lancet* 1911; **i**: 1572-1573
20. Committee on the Safety of Medicines (CSM) update: desensitizing vaccines. *BMJ* 1986: 293-298.
21. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987; **79**: 660-677.
22. Passalacqua G, Bagnasco M, Mariani G, Falagiani P, Canonica GW. Local immunotherapy: pharmacokinetics and efficacy. *Allergy* 1998; **53**: 477-484.
23. Tabar AI, Garcia BE, Rodriguez A, Olaguibel JM, Muro MD, Quirce S. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. *Allergy* 1993; **48**: 450-453.
24. Bousquet J, *et al.* Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998; **81**(5 Pt 1): 401-405.
25. Luigi A, Senna G, Mezzelani P, Pappalardo G. Safety of specific immunotherapy: a retrospective study. *J Investig Allergol Clin Immunol* 1994; **4**: 250-254.
26. Andre C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000; **121**: 229-234.
27. Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of SLIT in pediatric patients. *Allergy* 1999; **54**: 1110-1113.
28. Di Rienzo V, Minelli M, Musarra A, Sambugaro R, Pecora S, Canonica WG, Passalacqua G. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy* 2005; **35**: 560-564.
29. Fiocchi A, Pajno G, La Grutta S, Pezzuto F, Incorvaia C, Sensi L, Marcucci F, Frati F. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol* 2005; **95**: 254-258.
30. Tari MG, Mancino M, Monti G. Efficacy of SLIT in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergol Immunopathol (Madr)* 1990; **18**: 277-284.
31. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, Till SJ, Hamid QA, Nouri-Aria KT. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999; **341**: 468-475.
32. Jacobsen L, Nuchel Petersen B, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts. IV. Results from long-term (6-year) follow-up. *Allergy* 1997; **52**: 914-920.
33. Hedlin G, Heilborn H, Lilja G, Norrlind K, Pegelow KO, Schou C, Lowenstein H. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. *J Allergy Clin Immunol* 1995; **96**(6 Pt 1): 879-885.
34. Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. *Allergy* 1988; **43**: 523-529.
35. Frew AJ, Powell RJ, Corrigan CJ, Durham SR; UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; **117**: 319-325.
36. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; **60**: 4-12.
37. Penagos M, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, Canonica GW. Efficacy of SLIT in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006; **97**: 141-148.
38. Bufe A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, Braun W. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004; **59**: 498-504.
39. Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, Canonica GW, Passalacqua G. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003; **33**: 206-210.
40. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, Urbanek R, Valovirta E, Wahn U. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; **109**: 251-256.
41. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001; **107**: 469-476.
42. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, Rivas MF, Ribel M, Durham SR. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; **118**: 434-440.
43. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, Burastero SE, Calori G, Benetti L, Bonazza P, Puccinelli P, Parmiani S, Bernardini R, Vierucci A. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; **114**: 851-857.
44. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001; **31**: 1392-1397.
45. Bolhaar ST, *et al.* Efficacy of birch pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double blind food challenges. *Clin Exp Allergy* 2004; **34**: 761-769.
46. Pham-Thi N, de Blic J, Scheinmann P. Sublingual immunotherapy in the treatment of children. *Allergy* 2006; **61** Suppl 81: 7-10.
47. Pajno GB, Vita D, Caminiti L, Arrigo T, Lombardo F, Incorvaia C, Barberio G. Children's compliance with allergen immunotherapy according to administration routes. *J Allergy Clin Immunol* 2005; **116**(6): 1380-1381.
48. Malone DC, Lawson KA, Smith DH, Arrighi HM, Battista C. A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; **99** (1 Pt 1): 22-27.
49. Von Cauwenberge P *et al.* Consensus statement on the treatment of allergic rhinitis. European Academy of Allergy and Clinical Immunology. *Allergy* 2000; **55**(2): 116-34.