

EDITORIAL

Allergen immunotherapy in early childhood: between Scylla and Charybdis!

Giovanni B. Pajno

The prevalence of atopic diseases in childhood (asthma, atopic dermatitis and allergic rhino-conjunctivitis) has increased considerably in developed countries in the last 30 years [1, 2]. It has been argued that the increased awareness and improved ability to diagnose atopic diseases might account, at least in part, for this increase [3]. However, population-based studies using careful methods of ascertainment have also shown a real increase in the prevalence of atopic diseases in children [4–6].

The expression of allergic diseases may vary with age. In infancy, the main atopic manifestations are dermatitis, gastrointestinal disorders and recurrent wheezing, whereas, bronchial asthma and allergic rhino-conjunctivitis are the main problems in childhood. However, nowadays all the allergic diseases may begin very early in the life; rhinitis is strictly linked to asthma and both of them to atopic dermatitis [7].

Characteristically, sensitization evolves following this exposure order: food, indoor allergens and outdoor allergens. Recent prospective studies reported that early sensitization against hen's egg and house dust mites is highly predictive for the early appearance of clinical allergic diseases, persistent atopic dermatitis, asthma, rhinitis [8, 9]. As far as asthma is concerned, longitudinal studies starting from the first years of life have demonstrated that most patients who developed chronic persistent asthma at any age had exhibited their first symptoms and lower levels of lung function since their pre-school years [10]. In the light of this follow-up evidence, it should be argued that effective strategies for secondary prevention of allergic respiratory disorders have to be mainly based on early therapeutic interventions.

Immunotherapy (IT) represents, in selected patients, the only routine antigen-specific immunomodulatory treatment for immunologic-mediated diseases [11]. Subcutaneous IT (SCIT) is particularly effective in seasonal pollinosis [12], it improves seasonal asthma and inhibits seasonal increases in bronchial hyper-responsiveness [13].

In children, SCIT has been shown to prevent onset of new sensitizations [14] and to reduce progression of rhinitis to physician-diagnosed asthma [15]. SCIT confers long-term benefit for at least 3 years after its withdrawal [16]. The 'historical' studies with SCIT were performed in children aged from 3 to 14 years [17, 18] and neither serious side-effects nor life-threatening events had been reported. Nonetheless, a subsequent well-conducted trial reported severe asthma, generalized urticaria, angio-oedema and anaphylaxis in treated children below the age of 5 [19]. From then, the pre-school age is generally considered a prudent limit for IT in view of the possibility of severe side-effects. Indeed, this age is considered as a relative contraindication for SCIT [20] because severe side-effects are more difficult to treat in very

young children, and injection IT carries the risk of important untoward reactions [21].

Questions also arise regarding the potential psychological effects of IT. The emotional development and cognitive level of young children make them particularly vulnerable to potential psychological traumas from medical procedures. Children's cognitive abilities limit their capacity to define qualities such as intensity or duration in such situations and are more emotionally upset from minor traumas, such as venepunctures and injections [22].

According to recent studies, the sublingual immunotherapy (SLIT) seems to represent an effective alternative to SCIT, at least in childhood. In fact, it has been demonstrated to have long-lasting effects [23], and to inhibit seasonal increase of bronchial non-specific hyper-responsiveness in children [24].

In this issue of Clinical and Experimental Allergy, Di Rienzo and co-workers have provided evidence of SLIT safety in very young children, aged below 5 [25]. However, in the light of the new perspectives offered by allergy IT – both SCIT and SLIT; in terms of therapy timing, it is now important to establish some application rules for these time-consuming and often non-standardized procedures.

What is striking after reading articles and reviews concerning allergy IT is that its actual practice has not changed much [26]. Why is there such a disparity in the translation of our basic science knowledge [27] to this application treatment? The time is ripe to search for new paradigms [28]. Namely, in order to achieve successful results it is important to begin allergy IT in childhood, when bronchial asthma is not severe and children often show one or few sensitizations (Fig. 1)

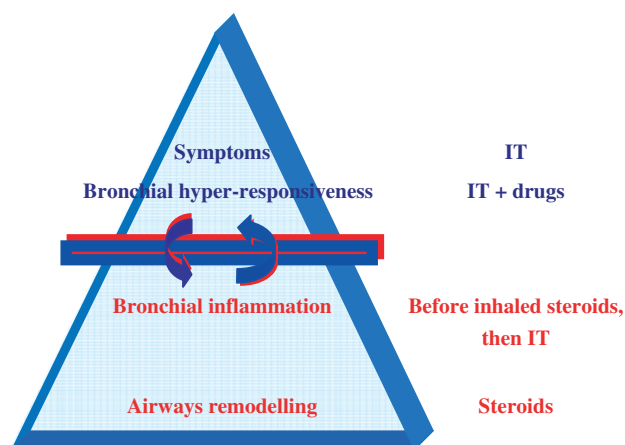


Fig. 1. The efficacy of immunotherapy (IT) is related to the careful selection of allergic asthmatic patients. To achieve successful results it is important to begin IT in childhood, when bronchial asthma is not severe and children often have one or few sensitizations.

Table 1. Allergy IT: key advances in childhood

1. The most suitable candidates for IT are children with allergic intermittent asthma
2. Children with mild-to-moderate persistent disease need prolonged therapies with anti-asthmatic controller drugs before beginning IT. Severe asthma is a contraindication for immunotherapy
3. Children suffering from rhinitis and asthma or with AR inadequately controlled by conventional anti-allergic drugs are also suitable candidates for IT
4. Patients with multiple sensitivities do not benefit from specific IT as much as do patients with a single sensitivity. Children with prevalent non-allergic triggers do not benefit from specific IT
5. In children suffering from AR, IT may reduce the incidence of asthma. Immunotherapy can prevent the onset of new sensitivities in cases mono-sensitized to house dust mites
6. SLIT is appropriate treatment for selected allergic patients, it is safe in pre-school children
7. Sociologic factors such as cost and economic rank of children's families should be taken into consideration

IT, immunotherapy; AR, allergic rhinitis; SLIT, sublingual IT.

IT actually is a cumbersome treatment, often non-standardized in application, with different perspectives in USA and in Europe. Therefore, it needs to be improved. However, as Di Rienzo and co-workers show, SLIT offers new possibilities for treatment of children. Similar results concerning the safety of SLIT are described by Fiocchi et al. [29] in allergic children aged 3–7 years.

In this field, it is mandatory 'to hold the right course' because we have to get over and overcome the strait, where two monsters 'Scylla and Charybdis' are threatening both young patients and physicians. Before prescribing IT in a young child, the major question (first monster) is whether his/her respiratory symptoms are secondary to either allergy or to other aetiological factors, such as cigarette smoke or viral infections.

Another pivotal question (second monster) is the impact of early treatment in toddlers without waiting the behaviour of their allergic respiratory symptoms. Careful selection of allergic children is the most important question to be faced, with the awareness that the early use of IT alters the natural history of the allergic diseases by suppressing airway inflammation at a time when a child is only intermittently symptomatic [30].

To overcome 'Scylla and Charybdis' means to defeat our reluctance to encourage the development of new strategies for asthma when the disease first manifests itself in early childhood. Achieving good results in the treatment of children is at present our clinical engagement, in my opinion we can open our minds to new paradigms [31] in order to carry out new evidence-based practice guidelines regarding this issue (Table 1).

Relief of allergic symptoms and long-lasting efficacy are two goals that can be attained in allergic children treated with IT. These effects are of particular relevance in paediatric patients where a preventive effect on the onset of asthma and a prolonged duration of this effect are expected: SLIT seems to meet this expectation, in association with an optimal safety profile.

References

- 1 Magnus P, Jaakkola JJ. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys. *BMJ* 1997; 314:1795–9.
- 2 Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994; 30:35–9.
- 3 Halken S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. *Pediatr Allergy Immunol* 2004; 15 (Suppl. 16):9–32.
- 4 Wieringa MH, Vermeire PA, Brunekreef B, Weyler JJ. Increased occurrence of asthma and allergy: critical appraisal of studies using allergic sensitization, bronchial hyper-responsiveness and lung function measurements. *Clin Exp Allergy* 2001; 31:1553–63.
- 5 Illi S, von Mutius E, Lau S et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001; 108:709–14.
- 6 Guilbert TW, Morgan WJ, Zeiger RS et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol* 2004; 114:1282–7.
- 7 Anonymous. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema: ISAAC – The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998; 352:1225–32.
- 8 Nickel R, Kulig M, Forster J et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997; 99:613–7.
- 9 Ohshima Y, Yamada A, Hiraoka M et al. Early sensitization to house dust mite is a major risk factor for subsequent development of bronchial asthma in Japanese infants with atopic dermatitis: results of a 4-year followup study. *Ann Allergy Asthma Immunol* 2002; 89:265–70.
- 10 Sears MR, Greene JM, Willan AR et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; 349:1414–22.
- 11 Norman PS. Immunotherapy 1999–2004. *J Allergy Clin Immunol* 2004; 113:1013–23.
- 12 Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991; 302: 265–9.
- 13 Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001; 107: 87–93.
- 14 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; 31:1392–7.
- 15 Moller C, Dreborg S, Ferdousi HA et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; 109:251–6.

- 16 Durham SR, Walker SM, Varga EM et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999; 341:468–75.
- 17 Aas K. Hyposensitization in house dust allergy asthma. A double-blind controlled study with evaluation of the effect on bronchial sensitivity to house dust. *Acta Paediatr Scand* 1971; 60:264–8.
- 18 Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children – a 14-year study. *Pediatrics* 1968; 42:793–802.
- 19 Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. IV. Systemic reactions according to the immunotherapy schedule. *J Allergy Clin Immunol* 1990; 85:473–9.
- 20 Bousquet J, Lockey R., Malling HJ World Health Organization Position Paper. Allergen immunotherapy: therapeutical vaccines for allergic diseases. *Allergy* 1998; 44 (Suppl. 53):1–42.
- 21 Ostergaard PA, Kaad PH, Kristensen T. A prospective study on the safety of immunotherapy in children with severe asthma. *Allergy* 1986; 41:588–93.
- 22 Peterson L. Coping by children undergoing stressful medical procedures: some conceptual, methodological, and therapeutic issues. *J Consult Clin Psychol* 1989; 57:380–7.
- 23 Di Rienzo V, Marcucci F, Puccinelli P et al. Long lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10 years prospective study. *Clin Exp Allergy* 2003; 33:206–10.
- 24 Pajno GB, Passalacqua G, Vita D, Caminiti L, Parmiani S, Barberio G. Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial. *Allergy* 2004; 59:883–7.
- 25 Di Rienzo V, Minelli M, Musarra A et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy* 2005; 35:560–4.
- 26 Casale TB. Status of immunotherapy. Current and future. *J Allergy Clin Immunol* 2004; 113:1036–9.
- 27 Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. *J Allergy Clin Immunol* 2004; 113:1025–34.
- 28 Holt PG, Sly PD, Martinez FD et al. Drug development strategies for asthma: in search of a new paradigm. *Nat Immunol* 2004; 5:695–8.
- 29 Fiocchi A, Pajno GB, La Grutta S et al. Safety of sublingual/swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol* 2005 (in press).
- 30 Li JT, Lockey RF, Bernstein IL et al. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 2003; 90:1–40.
- 31 Saxon A. What impact will the immune tolerance network have on the future treatment of allergic diseases? *Clin Exp Allergy* 2004; 34:1657–9.

Giovanni B. Pajno
 Department of Pediatrics – Allergy Unit
 Faculty of Medicine
 University of Messina
 Via Consolare Valeria
 98125 Messina
 Italy
 E-mail: Giovanni.Pajno@unime.it