Guglielmo Scala

Real-life approach to allergen immunotherapy for respiratory diseases in childhood

U.O.S.D. Allergologia Loreto Crispi, Napoli - Italy - E- mail: guglielmoscala@gmail.com

Key words

Allergen-specific immunotherapy, real-life, pediatric allergy

Corresponding author
Guglielmo Scala
U.O.S.D. Allergologia
Loreto Crispi, Napoli
E-mail: guglielmoscala@gmail.com

Summary

Allergen-specific Immunotherapy (AIT) is a well-documented etiological therapy for IgE-mediated rhinitis and asthma and it is the only treatment strategy able to alter the natural history of the diseases. This review aims at focusing some real-life aspects of AIT. In spite of the high level of evidence for efficacy and safety reached by AIT and the continuously improving quality of allergenic extracts, it is estimated that, with regional variations, less than 5% of European children with AR are treated with AIT. The number of AIT prescriptions is decreasing in these last years in all Europe. The adherence to the treatment is quite low today either for SCIT or for SLIT. The results of clinical trials shouldn't be referred to AIT in general but rather to the specific product utilized. There is the need for a closer cooperation among allergists with other specialties in order to optimize the assessment of allergic patients and of AIT.

Worldwide, allergic rhinoconjunctivitis (AR) and bronchial asthma (BA) are a major health problem because of their high prevalence, chronic course and worsening trend. This is particularly true in pediatric age. In the last decades of the XX century the International Study of Asthma and Allergies in Childhood (ISAAC) demonstrated that allergic rhinoconjunctivitis has an average prevalence of 7.2 % for the 6 to 7 year age group and 16.6% for the 13 to 14 year group (1). Asthma prevalence in children ranges from 5 to 10 %. Asthma and allergic rhinitis affect the same tissues, involve common inflammatory mechanisms, cells and mediators and are frequently found together (2). Most children with AR suffer from concomitant asthma symptoms, consistent with the theoretical approach of "one airway - one disease". Furthermore AR and BA are believed to be next steps of the so-called "allergic march". Not all allergic patients actually "march" along their own allergy from rhinitis to bronchial asthma, however the concept still is of outstanding importance because it focuses patients' and physicians' attention on the central role played by prevention. Allergen-specific Immunotherapy (AIT) is a well-documented etiological therapy for IgE-mediated rhinitis and asthma and is considered the only treatment strategy able to alter the natural history of the diseases. It is the only known treatment that modifies the immune response and treats the cause rather than the symptoms (3). Nevertheless it is estimated that, with regional variations, only 1 to 5% of European children with AR are treated with specific immunotherapy (AIT). About 75% of these children have subcutaneous injections (SCIT) of allergen extracts with 25% using sublingual drops or tablets (SLIT) (4). The small percentage of allergic children treated with AIT is probably the main problem al-

lergists will have to face in the next years: the ultimate sense and the survival itself of allergology and immunotherapy.

Allergic rhinitis and bronchial asthma in children. From diagnosis to AIT prescription

What we call pediatric age is something that ranges from newborns and infants up to eighteen year-old subjects. Hence the diagnosis of respiratory allergies should take in account different parameters depending of patient's age. The classical symptoms of AR are nasal obstruction, itching, sneezing and running nose that may be present isolated or together. Eye symptoms are often present too, such as redness, itching and lachrymation. According to ARIA classification, symptoms may be persistent or intermittent depending by their duration and mild or severe depending on how seriously they interfere with patient's everyday life (5). In the cold season symptoms of AR may be difficult to distinguish from those due to upper airway infections, both events contributing to the final clinical picture.
More problematic is the diagnosis of BA. Since asthma differs throughout childhood, preschool children, school-age children and adolescents should be examined separately. In the school-aged patients and older it is usually possible to perform respiratory functional test in order to assess the presence of a reversible airway obstruction. However, there is a poor relationship between the symptoms experienced by patients and objective lung function, and asthma is often misdiagnosed. In addition, lung function tests can be insensitive and are especially difficult to perform reliably in children (2). There is evidence that there is too much delay before asthma diagnosis is made. Delays of 18 months have been reported in children (6). The diagnosis of asthma is mainly based on clinical parameters, i.e. an accurate clinical history and a careful physical examination. For both allergic asthma and rhinitis the cornerstone for the diagnosis is the demonstration of specific IgE against one or more relevant environmental allergens. Specific IgE can be detected both in vitro and in vivo. Skin prick test (SPT) with a standard panel of environmental allergens extracts should represent the first diagnostic step. SPT are highly reliable, cheap and give answers within few minutes. Other diagnostic tools such as nasal cytology, Component Resolved Diagnosis, and exhaled nitric oxide, are of great interest but may be confined in a second level, specialist approach.

Efficacy of AIT

The evaluation of the clinical efficacy of AIT in children has long been a controversial topic, mainly because high quality pediatric RCTs are few. Meta-analyses have produced controversial results, thus it is time to review this area focusing on the few high quality recent data rather than just relying on a meta-analysis approach (4). SCIT still is the primary form of immunotherapy in children in most European countries. The preventive asthma study (PAT study) (7) has been conducted on children with AR and allergic to grass or birch pollen. At the 10-years follow-up it has been shown that SCIT is effective for children with hay fever and can prevent the onset of asthma (8). Three recent well-designed randomized controlled trials have demonstrated subcutaneous SCIT to be safe and effective in asthmatic children allergic to grass pollen (9), to Alternaria (10) and to HDM (11). The efficacy of SLIT in AR in children has been demonstrated by a large number of high quality pediatric trials in which allergen drops or tablets were used (12 - 15). A preventive effect on the evolution toward bronchial asthma has been observed (16) in a small number of patients. In a recently published study a population of at high-risk infants has been treated with the sublingual administration of a mixture of soluble allergens. The mixture comprised 3 x 200 mL aliquot extracts, respectively, of house dust mite, cat and timothy grass, given daily for 12 months. The primary efficacy end point was the proportion of participants sensitized to >1 allergen, to be assessed 3 years post-treatment but no significant differences in immunologic parameters between active- and placebo-treated patients were detected (17). Other ongoing trials are exploring the possible role of AIT in primary or secondary prevention.

Indication for AIT in childhood

There is not a general agreement about the indication for AIT in children. The GINA guidelines (18) give little room for AIT in asthmatic patients, limiting its use to those patients in which the environmental control and the standard pharmacotherapy failed but it can be argued that it doesn't make much sense to consider AIT as a sort of last chance to be utilized in patients with a more severe condition as suggested by the GINA guidelines. Patients with a long history of asthma or rhinitis have likely gone through an irreversible structural tissue remodeling and have often developed one or more co-morbidities such as

sinusitis or gastro-esophageal reflux. Those patients are far less likely to respond to an IgE-specific immunotherapy. IgE-related mechanisms are known to drive the first steps of the pathogenesis of allergic diseases. Hence, an early AIT treatment is expected to give better result. The Italian Society of Pediatric Allergy and Immunology produced a document in 2010 (19) in which AIT is suggested in virtually all children with BA or AR in order to try and prevent the worsening of the disease and to reduce the risk of developing asthma. A recent EAACI position paper suggests that AIT should be started early in the disease process even in children with well-controlled allergic symptoms (20). The ARIA guidelines (5) suggest AIT in allergic patients with rhinitis with or without asthma (strength of recommendation "A"). AIT is indicated in childhood when a few parameters are verified. A complete diagnostic pathway must confirm the diagnosis of AR and/or allergic bronchial asthma. The relevant allergen(s) must be identified and demonstration occurs that the presence of the allergen(s) is strictly related to the appearance of symptoms. The duration of the disease should be of at least one year. The allergen extract should be available and standardized.

The quality of the extracts

Allergen companies and available allergen extracts are many. To date most children in Europe are treated with allergen products that have not obtained a marketing authorization (20). By utilizing the term "AIT" we run the risk we're doing an intellectual mistake. Today the term "AIT" taken in general sense doesn't mean so much. Allergen extracts made by different factories are much different products, not even comparable among them neither for purification nor for concentration. Each company utilizes an its own in-house standardization which has the sole purpose of ensuring that marketed allergen lots be identical. This means that experimental results obtained with one particular brand merely refer to the brand utilized in that trial and can't be extended to other brands (21,22). More, one must remember that that clinical results (whatever they are) have been obtained with that particular allergen dosage, that schedule of utilization, that duration of treatment and all this in those patients who fall inside the trial inclusion criteria, that for the randomized controlled trials are usually quite narrow and far from the real-life patients. The correct AIT prescription should be driven by nothing but the weight of the evidence for each single product. Schedule, dosage and timing of the therapy must strictly respect the manufacturer instructions.

SCIT – SLIT

In real life the choice between SCIT and SLIT should not be an issue. Both SCIT and SLIT have reached a satisfactory level of evidence and the choice should take into account other aspects of patient's family everyday life. Both SLIT and SCIT have pro e cons. SCIT is performed at doctor's office and therefore requests the patient and at least one of his or her parents to lose some hours every three to five weeks, then is obviously less appreciated by children (who should be asked to give their own informed consent), and is more likely to give adverse effects. On the other hand SCIT may create a better relationship between patients and doctor with a positive effect in term of clinical assessment, therapy adjustment and adherence. SLIT is performed at home, does not require the family to move and has a better safety profile but drops or tablets have to be taken every day for months or years, that is easier said than done. Parents have the responsibility of the management of the therapy and may find themselves in troubles if children for example have fever or are submitted to dental treatments or present vomiting shortly after having taken the vaccine and so on. In those cases they have to refer to the doctor. Other points to be considered are the social, economic and instruction level of the patient's family and the distance between the home and the clinic. SCIT is something cheaper than SLIT but you have to add the costs of the journeys to and from the clinic. Doctors must describe accurately the two possibilities to the families and must help them to a better understanding. The final choice should be taken together.

Optimal Duration of AIT

When prescribing AIT to allergic children we expect to obtain two main results. The first one is to obtain a clinical benefit, in terms of symptoms and drug consumption reduction and to give our patients a better quality of life. In this sense AIT works as an effective anti-symptomatic drug (23) and the effects of the therapy are early recognizable and significant, even by the first season of treatment (12,13) The second result we expect is a long-term

clinical efficacy that could last beyond the treatment period. In recent years, the long-lasting effect has in fact been demonstrated for SLIT and it is also known that the duration of the effect is partially dependent on the duration of AIT itself (24). A long-term efficacy over 2 years following a 3-year therapy has been demonstrated in adults (25) and it can be speculated that, because the immune response of children during the first year of SLIT strongly correlates with that of adults, the long-term efficacy data for adults can be extrapolated to children (4). Further information comes from an open, real-life Italian study in which different treatment periods were compared. Patients with AR and/or mild bronchial asthma underwent a 3-year, 4-year or 5-year course of SLIT. This long-lasting survey showed that a long-term effect (>4 years) of SLIT exists and correlates to the duration of treatment and that the optimal duration of SLIT to achieve a long-lasting effect is 4 years because the fifth year of treatment adds only marginal additional benefits (26). The available literature suggests that a 3-year duration of treatment maintains the efficacy on allergic symptoms for at least an equivalent period of time. Some recent meta-analyses have examined data concerning the relationship between duration of therapy and long-lasting outcomes. Even though the issue remains to be further evaluated in the future, the duration of AIT needed to guarantee long-term efficacy after stopping the treatment is generally agreed to be 3 years (3, 27). One review (28) claims AIT to be effective only in the first year of treatment and that continuing the therapy doesn't add any further but it is to notice that this particular outcome doesn't appear to be the result of a meta-analytic examination of the available data.

The adherence to treatment

The treatment of AR and BA, as many chronic diseases, is affected by the adherence problem. Adherence may be defined as 'the extent to which a person's behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds to the recommendations agreed with a health care provider' and deals something better with real life situations than did the term compliance because of the authoritative and paternalistic connotations of the latter one. Nonadherence to medication regimens seriously affects the quality and length of life. Poor adherence to medication regimens accounts for substantial worsening of disease, death, and increased health care costs (29). As for AIT, one-century experience with immunotherapy, together with experimental data and meta-analyses results suggest that the best effect of AIT is reached when the therapy is prolonged for some years without interruptions and at that least 3 years of treatment are required to obtain the long-term benefits and disease-modifying effect. However, both clinical trials and real-life studies have shown that treatment persistence and compliance are frequently problematic, particularly in real-life. This will jeopardize the (cost-) effectiveness of immunotherapy and implies that a significant proportion of resources are invested without achieving the maximum benefit (30). In a recent Italian study, with sales data provided by two major manufacturers, more than 50% of patients discontinued SLIT during the first year, and only 13% were still on treatment in the second year (31). Two recent surveys, conducted among specialists, reported that the absence of perceived efficacy of the treatment was the most frequent reason for withdrawal, followed by cost and tolerability, whereas side effects, patients' education and ease of use were judged to be not particularly relevant to adherence. (32,33). The frequency of controls at doctor's office may be relevant as suggested by one study in pediatric patients in which the better adherence, although not optimal, was found with control visits performed every 3 months (34). The Italian Government Health Plan 2011 – 2013 prescribes that AIT use for respiratory allergies in children must be implemented in order to prevent the worsening of the diseases (35). In real life this means better and more detailed information, especially concerning the efficacy, and a closer patient–physician relationship, but it also means that the Health System is expected to play an active role in this scenario.

Reduction of AIT prescription. "The Mother of all the Real-Life Issues"

In the last years we have been witnesses of a scientific paradox: The basic and clinical studies on atopy and allergic diseases have improved in quality and progressively grown in number. Many systematic reviews and meta-analyses have been published on the efficacy and safety of the AIT in the treatment of AR and bronchial asthma and international guidelines and position papers agree in recommending AIT for the treatment of AR and BA. Nevertheless at the same time AIT prescriptions have decreased in number everywhere in Europe by a trend of about 10% pro year. The stronger the clinical evidence the

less the prescriptions. In Italy the whole country mean difference is 10.4% between 2011 and 2012 and 21% between the first semester 2012 and the same period 2013. This means thousands of therapy units lost per year (www.assobiomedica.it). The rate of decrease is such as to create concern about the mere survival of AIT itself, at least in some countries, and I do believe that the destinies of AIT and of Allergists are closely linked.

The current interpretations for such decline are the economical international crisis and the low pollen counts registered in Europe in the last years. These two points, even though undoubtedly true, do not represent the whole truth. A deep examination of the problem is beyond the scope of this review but some points may be outlined. A wide disagreement exists among specialists about AIT utilization in rhinitis and asthma. Allergists, pulmonologists and ENT specialists have a different scientific background and different approaches to the AIT. One of the reasons might be found in the fact that meta-analyses are double-edge blades. By one hand meta-analyses have given AIT the strength of the highest possible evidence, but on the other hand the meta-analyses themselves present several point of weakness like the high heterogeneity, the low quality level of many trials and the small number of pediatric trials. This, in turn creates uncertainty among primary care doctors (GPs and Pediatricians) and may discourage them in prescribing AIT.

One solution, among many, might be found in a better cooperation among allergists, GPs and pediatricians. Allergists should make an effort to improve the knowledge of clinical allergy among the pediatricians and GPs and to optimize the first level diagnostic procedures and treatment, including AIT, by means of short practical courses in which doctors may approach the management of skin testing and of the AIT procedures. Another urgent need is to go outside the boundaries of the scientific world and to utilize the *media* to bring a correct information about respiratory allergies and the therapeutic role of AIT at the general population level in order to stem the thousands of incorrect non-scientific opinions about "vaccines" that circulate on the media and the web. A better and more detailed education, especially concerning the efficacy, and a closer patient–physician relationship are realistic and achievable goals. If we succeed in getting those results we'll have done something good for the patients suffering from allergic diseases and at the same time we'll have helped our specialty not to disappear.

References

1. Strachan D, Sibbald B, Weiland S et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Pediatr Allergy Immunol 1997;8:161–76.
2. Holgate S, Bisgaard H, Bjermer L, Haahtela T, Haughney J, Hornee R, McIvor A, Palkonen S, Price DB, Thomas M, Valovirta E, Wahn U. The Brussels Declaration: the need for change in asthma management. Eur Respir J. 2008; 32:1433–1442
3. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010;(12):CD002893.
4. Bufe A, Roberts G. Specific immunotherapy in children. Clin Exp Allergy. 2011 Sep;41(9):1256-62
5. Bousquet J, Khaltaev N, Cruz AA, et al.; World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 (Suppl. 86):8-160.
6. Haahtela T. Early treatment of asthma. Allergy 1999; 54, Suppl. 49:74–81.
7. Möller 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.
8. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007,62:943–8.
9. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol. 2006;117:263–8.
10. Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children. J Allergy Clin Immunol. 2011;127:502-8.
11. Zielen S, Kardos P, Madonini E. Steroidsparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. J Allergy Clin Immunol. 2010; 26:942–49.
12. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and effi cacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy J Allergy Clin Immunol. 2009;123:167-73.
13. Wahn U, Tabar A, Kuna P, et al. Effi cacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis J Allergy Clin Immunol. 2009;123:160-6.
14. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol. 2011;127:64e71, e1ee4.
15. Wahn U, Tabar A, Kuna P, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2009; 123: 160e166.e3.
16. Novembre E, Galli E, Landi F et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2004; 114:851–7.

17. Holt PG, Sly PD, Sampson HA, Robinson P, Loh R, Lowenstein H, Calatroni A, Sayre P. Prophylactic use of sublingual allergen immunotherapy in high-risk children: A pilot study. J Allergy Clin Immunol. 2013;132(4):991-993.
18. Global Initiative for Asthma: global strategy for asthma management and prevention: updated December 2012 (http://www.ginasthma.org/uploads/users/files/GINA_Report_2012.pdf).
19. Duse M, Minasi D, Pajno G, Pifferi M, Scala G, Terracciano L, Tosca M. Immuno-Terapia allergene-Specifica: se, quando, come eseguirla. Revisione della letteratura e indicazioni. Documento della Commissione ITS della SIAIP. Riv It Allergol Ped. 2010;1:1-29.
20. Calderon MA, Gerth van Wijk R, Eichler I, Matricardi PM, Varga EM, Kopp MV, Eng P, Niggemann B, Nieto A, Valovirta E, Eigenmann PA, Pajno G, Bufe A, Halken S, Beyer K, Wahn U. Perspectives on allergen-specific immunotherapy in childhood: An EAACI position statement. Pediatr Allergy Immunol. 2012;23:300–306.
21. de Bot CM, Moed H, Berger MY, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. Pediatr Allergy Immunol. 2012: 23: 149–57.
22. Bachert C, Canonica GW, Bufe A. SIT: efficacy depends on product, not on route of application. Pediatr Allergy Immunol. 2012;23:401.
23. Matricardi PM, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. J Allergy Clin Immunol. 2011 Oct;128(4):791-799.e6.
24. Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, et al. Longlasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy. 2003;33:206-10.
25. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al.Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol. 2010;125:131-8, e1-7.
26. Marogna M, Bruno M, Massolo A, et al. Long-Lasting effects of sublingual immunotherapy for house dust mites in allergic rhinitis with bronchial hyperreactivity: a long-term (13-year) retrospective study in real life. Int Arch Allergy Immunol. 2007;142:70-8.
27. Calderón MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. J Allergy Clin Immunol. 2011; 127(1): 30-8.
28. Di Bona D, Plaia A, Scafidi V, Leto-Barone MS, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. J Allergy Clin Immunol. 2010;126:558-66.
29. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487-97.
30. Kiel MA, Röder E, Gerth van Wijk R, Al MJ, Hop WCJ, Rutten-van Mölken MPMH. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol. 2013;132:353-60.
31. Senna GE, Lombardi C, Canonica GW, et al. How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers viewpoint. J Allergy Clin Immunol. 2010;126:668-9.
32. Passalacqua G, Frati F, Puccinelli P et al. Adherence to sublingual immunotherapy: the allergists' viewpoint. Allergy. 2009; 64:1795–6.
33. Scurati S, Frati F, Passalacqua G, Puccinelli P, Hilaire C, Incorvaia C. Adherence issues related to sublingual immunotherapy as perceived by allergists. Patient Prefer Adherence. 2010; 4:141–5.
34. Vita D, Caminiti L, Ruggeri P, Pajno GB. Sublingual immunotherapy: adherence based on timing and monitoring control visits. Allergy. 2010; 65:668–9.
35. Piano Sanitario Nazionale 2011 – 2013. Ministero della Salute. http://www.salute.gov.it/imgs/C_17_pubblicazioni_1454_allegato.pdf.