

INVITED REVIEW

Specific immunotherapy in children

A. Bufer¹ and G. Roberts²

¹Department of Experimental Pneumology, Ruhr-University Bochum, Bochum, Germany and ²Respiratory Biomedical Research Unit, Developmental Origins of Health and Disease, University of Southampton School of Medicine, Southampton, UK

Clinical & Experimental Allergy

Summary

Subcutaneous immunotherapy (SCIT) with allergen extracts in children with allergic rhinitis, with or without co-seasonal asthma, has developed into a routine treatment although the scientific evidence for its efficacy is not as strong as for adults. In the hands of experienced allergists, this treatment has been proven to be safe. The development of allergen tablets for sublingual immunotherapy (SLIT) may open a new age of more convenient, safer SIT. In children, in particular, the evidence for the long-term efficacy of SLIT, its ability to prevent the development of asthma and polysensitization and its comparability to SCIT will be required before it will replace the traditional subcutaneous route. Issues of compliance represent an important drawback of SLIT. We need ways of improving this. Treatment of asthma by immunotherapy is still restricted to clearly defined patients with mild to moderate asthma with symptoms that are related to the specific allergen sensitization. In these patients, symptoms and use of anti-inflammatory therapy can be reduced by SIT.

Keywords children, immunotherapy, prevention, SCIT, SIT, SLIT

Submitted 10 December 2010; revised 24 January 2011; accepted 15 February 2011

Correspondence:

A. Bufer, Department of Experimental Pneumology, Ruhr-University Bochum, Bochum, Germany.

E-mail: albrecht.bufer@rub.de

Introduction

From the early days of specific immunotherapy (SIT), it was taken for granted that tolerance induction by injecting allergens subcutaneously would be more effective in allergic children than adults. A WHO working group in 1989 stated that 'remission is more likely to occur in children than in adults, but immunotherapy is less well tolerated in small children and is seldom indicated below 5 years of age' [1]. The scientific basis for this statement, although written three decades ago, is still relatively small. Nevertheless, treating children with SIT has now become a routine practice world-wide. This review will attempt to summarize present data about the use of SIT in children. Epidemiological aspects, immunological mechanisms, prevention and application measures, efficacy, side-effects and compliance will be covered.

Use of specific immunotherapy in children

World-wide, the International Study of Asthma and Allergies in Childhood (ISAAC) demonstrated in the 1990s [2] that allergic rhinoconjunctivitis (AR) or hayfever have an average prevalence of 7.2 % for the 6–7-year age group

(range 0.0–34.9%) and 16.6% for the 13–14-year group (range 0.0–54.4%). Ten years later, the prevalence had only seen a small increase in the 6–7 age group with a slightly larger increase in the older age group [3]. This data is similar to the results of a German survey (KiGGS) that demonstrated a hayfever life-time prevalence of 4.9% for age group 3–7, 14.4% for age group 11–13 and 18.4% for age group 14–17 years [4, 5]. About 40–60% of children with AR suffer from concomitant asthma symptoms [6]. It is estimated that with regional variations, 1–5% of European children with AR are treated with SIT. About 75% of these children have subcutaneous injections [subcutaneous immunotherapy (SCIT)] of allergen extracts with 25% using sublingual drops, sprays or tablets [7]. SIT of children with only bee venom allergy, wasp venom allergy or allergic asthma is rare. Recently, promising data on specific oral tolerance induction (SOTI) for food allergies associated with severe symptoms has been published although it currently still needs to be regarded as experimental approach [8, 9].

As in adults, allergen extracts for subcutaneous application (SCIT) are prepared individually and distributed via the pharmacies or the companies directly. According to the European and national immunotherapy position

papers and guidelines [10–12], best practical and long-term experience in children is observed with a 3 years treatment phase with or without co-seasonal reduction. Some companies provide only pre-seasonal treatment schedules; novel developments even suggest that only three to seven injections once a year are effective [13]. No scientific but only poor anecdotic data exists to compare all these different schedules for efficacy in children. Only by looking at the reliable 1-year studies with allergen tablets in children which are applied pre- and co-seasonal and stopped after 6 months by average one might state that efficacy can be achieved already 3–6 months after beginning of treatment [14, 15], an observation which is described and summarized by Akdis and Akdis [16] also for adults.

Conventionally, therapy starts with an induction phase including once or twice weekly injections. This phase normally lasts 8–12 weeks when children enter the maintenance phase in which they have injections every 4 weeks over 3 years. Before every injection, the child has to be assessed for symptoms or signs of infection, recent allergic reactions, asthma or other symptoms and also any concurrent medication including vaccinations. The injection should be given by the experienced and qualified health professional. Injections are given into the subcutaneous tissue in the lower third of the lateral upper arm, always changing from the left to the right. After injection, the child has to stay in the clinic for at least 30 min (60 min in the United Kingdom) since it is known that all severe systemic reactions occur during this phase. The medical staff in attendance should be trained in and prepared for management of an anaphylactic reaction.

Sublingual immunotherapy (SLIT) is prescribed for home application although it is recommended that the first dosage is given under medical observation in the clinic because nearly all systemic reactions are observed with the first application. To maximize concordance with therapy, it is recommended to prescribing a maximum of 30–60 days of therapy, reviewing the child before re-prescribing. As with SCIT, allergen dosage may be increased during an induction phase although with allergen-tablets treatment is usually started at the maintenance dosage. Interestingly, it was shown that omitting this up-dosing strategy does not lead to more side-effects than without [17, 18].

Indications for specific immunotherapy in children

SIT in children is indicated for nearly identical reasons as in adults [12]: at least a 1 year history of AR with or without co-seasonal asthma treated with symptomatic drugs, evidence of sensitization towards a relevant allergen either by skin prick test or elevated allergen-specific IgE, clear evidence for clinical relevance of the disease-

Table 1. Indication for specific immunotherapy (SIT) in children

Medical history	At least 1 year medical history of allergic rhinitis (AR) with or without co-seasonal asthma treated with symptomatic drugs
Sensitization	Evidence of sensitization towards a relevant allergen either by skin prick test or elevated allergen-specific IgE (in small children, IgE would be sufficient for diagnosis)
Clinical relevance	Evidence for clinical relevance of the disease-related allergen (eventually by standardized provocation testing)
Allergen extract	Availability of a standardized allergen extract or preparation registered or approved by the authorities

related allergen and the availability of an approved, standardized allergen extract (see also Table 1).

Recently it was decided by the European Medicines Agency (EMA) that for allergen extracts to be registered in Europe, a paediatric investigational plan (PIP) has to be presented by the respective company. This PIP has to include the performance of clinical studies in children with every extract which will be applied for registration. Clinical data does not need to be presented if biological equivalence with related extracts which have already been tested effective in clinical studies can be demonstrated. An open question is how far clinical studies have to include long-term efficacy data also in children [19]. With this approach, it can be expected that all allergen extracts for SIT will be registered by the authorities on the basis of efficacy and side-effect data by clinical studies for children and adults in the next decade.

Efficacy of specific immunotherapy in children

The evaluation of the clinical efficacy of SIT in children has become a controversial topic, mainly because there are only a very few randomized, double-blind, placebo-controlled studies, with high methodological standards, that have only included children. Therefore, a systematic review on SIT in children with AR from 2008 came to the conclusion that the evidence for the efficacy of SCIT is conflicting and that for SLIT is missing [20]. SCIT is the primary form of immunotherapy in children in most European countries. No new clinical evidence for the efficacy of SCIT in children was been recently published but there are now a number of new studies with SLIT using allergen tablets. It is therefore time to review this area again focusing on the high quality recent data rather than just relying on a meta-analysis approach. A cost-benefit analysis of SIT compared with symptomatic therapy is also an important consideration although this is beyond the scope of this review.

Efficacy of subcutaneous immunotherapy

Already in the late sixties, Sanders [21] presented evidence for the efficacy of SCIT using a depot preparation in 32 grass pollen allergic children with hayfever and asthma. This study took a randomized, double-blind, placebo-controlled analysis approach and would be still viewed a high quality standard study. In the same year, an American group published a study in children using an aqueous ragweed extract for the treatment of hayfever [22]. The study did not show efficacy for this end-point perhaps because the authors used aqueous solutions with relative low dosage or because of their heterogeneous subject group. In a study from Canada in 1979, ragweed sensitized children were treated with a tyrosine-adsorbed extract, again a different allergen preparation which was already in adults not proven to be as effective as expected [23]. The results were not clear cut and it is judged to be a low quality study. Two other paediatric-only studies for SCIT in hayfever had an open design and are therefore assessed as being of low quality [24, 25]. They used mould and mite extracts for treatment, both allergens which also showed little efficacy adults. The preventive asthma study (PAT study) has been published more recently; as well as demonstrating that SCIT can prevent the onset of asthma, it shows that SCIT is effective for children with hayfever [26]. SCIT treated children showed significantly less nasal symptoms after 2 and 3 years of therapy as measured by visual analogue score. As children in this study were randomized but the intervention was not placebo-controlled and efficacy of treatment was not a primary end-point, it is viewed as a low quality study in terms of efficacy of SCIT in hayfever. The number of children treated, however, was significantly higher than other studies and a control group was included. Additionally, children with asthma were excluded at enrolment and nasal symptoms were only mild to moderate. It is known from adult studies that the efficacy of SCIT in mild to moderate AR only becomes apparent after a long period of treatment.

To obtain a complete picture of data on efficacy of SCIT in children, adult studies that also enrolled teenagers should be evaluated. For the Cochrane meta-analysis on the efficacy of SCIT in AR, 15 studies were selected for the evaluation [27]. Five studies enrolling adults and teenagers fulfilling the inclusion criteria of the review treated 99 patients compared with 92 controls. The standardized mean difference (SMD) of these five studies was -1.54 in favour of treatment which is greater than the SMD of all 15 studies (-0.73). Of course, these data have to be carefully evaluated as the heterogeneity between studies is very high. It does though indicate that teenagers treated with SCIT seem to benefit at least as much as adults. In summary, the evidence for the efficacy of SCIT in children is small but there is some strong evidence that immu-

notherapy by injection, especially in AR caused by pollen allergens, is effective.

There are also minimal data on treatment of asthma caused by inhaled allergens such as mites. Efficacy has been demonstrated in randomized, double-blind, placebo-controlled studies for grass pollen-induced asthma [28] and, very recently, with mite allergic children with asthma using an allergoid preparation [29]. In the mite study, SCIT demonstrated significant reduction in the use of inhalant corticosteroids in the treatment group compared with the control one indicating that SCIT may have a positive influence on the course of asthma in children.

Efficacy of sublingual immunotherapy

The scientific evaluation of SLIT in children started later than that for SCIT so, in general, it benefits from studies with better methodologies. These data have been evaluated in a 2003 Cochrane analysis [30], a 2006 meta-analysis of studies only involving children [31], a 2008 systemic review [20] and a further more recent meta-analysis [32]. The early data provided evidence for efficacy of SLIT in adults, especially for treatment of AR in pollen allergic patients. No reliable long-term efficacy results were available at that time. Treatment of children with SLIT was said to be ineffective because there were minimal study data with inconsistent results. Later studies echoed these results demonstrating no efficacy or, at times, efficacy only in a subgroup analysis [33, 34]. The authors of the 2006 meta-analysis did though conclude that SLIT in children was effective [31]. They have been criticized for giving too much weight to studies with low methodological quality [35]. If single studies are focused on, SLIT can be shown to be effective after 2–3 years of treatment [36], in subgroups with moderate to severe nasal and eye symptoms [33], and in certain secondary end-points such as bronchial hyperreactivity [34]. At that time, there was insufficient data from long-term studies, with more than 1 year placebo treatment, as well as from well powered head to head studies with SCIT. One observation at that time did demonstrate that the efficacy of SLIT increased in dose-dependent manner indicating that high dose preparations were more effective than low dose ones [37].

The turning point at that stage was the introduction of allergen tablets for sublingual treatments which went through a standard registration process in the European market being evaluated like classical pharmacological medications. These were two tablets with grass pollen extracts, one with a mixture of five different grasses [15, 38] (Oralair[®], Stallergenes, Antony, France) and one with only one grass [14] (Grazax[®], ALK-Abelló, Hørsholm, Denmark). It was demonstrated that both were effective in adults when treatment was started at least 8 weeks before the season, that both showed increasing efficacy in

symptoms and use of rescue medication over 3 years of treatment [37, 39] and that both were effective in children and adolescence from 5 to 18 years when therapy was performed pre- and co-seasonal for 1 year [14, 15]. All this data led to registration of both tablets on the European market for adults and children. Interestingly, one of the studies demonstrated a significant improvement of co-seasonal asthma in children [14]. For one tablet, long-term efficacy in adults over 2 years following a 3-year therapy could be demonstrated [40]. 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 [14].

Developing immune system in children

Pharmacokinetic and pharmacodynamic data demonstrate that drugs in children often behave differently compared with adults. For immunotherapy with allergens this has never been scientifically analysed. There are no reliable data on absorption, metabolism and secretion of allergens in adults, let alone children. Although the mechanisms of SIT are being increasingly understood, the immunological data have been mainly generated in adults and animal models [16]. There is some evidence that during immunotherapy, the IgE and IgG/IgG4 responses in children is comparable to adults [41]. Children seem to be more sensitive to immunomodulation by natural allergen exposure as well as by treatment with allergen extracts. This is likely to be merely a dose-response effect given that children usually receive higher dosage per body weight than adults as demonstrated for SLIT with grass pollen tablets. In this context, it is interesting to ask whether the humoral and cellular immune response in children is functionally comparable to that of adults. The available data on the development of the infant and child immune system clearly indicates that by 5 years of age, the repertoire of T and B cells as well as number of antigen presentation cells and the different antibody levels have already reached a comparable state to adulthood [42]. T and B cell development starts at 12 weeks after conception mainly in the liver; frequencies of both populations already reach a relatively high level at birth, only the number of naive compared with activated cells is still higher at that time. Until the age of 5 years, a great deal of T and B cells are activated and the number of memory cells has reached a substantial level. Infant IgM-, IgA- and IgE-antibody production starts shortly after birth whereas IgG antibodies are only increased at that time because of trans-placental transfer of maternal antibodies. By the age of 5 years, children produce a broad spectrum of all isotypes indicating that the response towards a therapeutic vaccination, such as immunotherapy, may lead to a comparable response as in adults.

Side-effects and compliance

In the early days of SIT, it was stated that children experience more side-effects than adults. As similar dosages of allergens are used in children and adults, it might be expected that the higher relative dosage would result in children having more side-effects. The few reliable studies on SCIT side-effects have never confirmed this. In both children and adults, all systemic anaphylactic reactions occur during the first 30 min after injection leading to the general obligation that patients have to wait in the clinic for at least 30 min (60 min in the United Kingdom) after SCIT to ensure that anaphylaxis is treated as soon as possible [43]. According to a report of the German authorities on deaths during SCIT, nearly all of these events were due to medical error with wrong dosages, mix up of charges and intravenous injection [44]. The risk for systemic reactions in children when treated subcutaneously is not well documented but some factors such as severe asthma attacks, elevated allergen exposure during therapy and concomitant diseases such as severe infections should be taken into account when using SCIT. Inexperience of the doctor with SCIT is another recognized risk factor which led the authorities to demand that SCIT is only utilized by personal with experience in immunotherapy and in emergency medicine.

The risks of SCIT are one of the drivers for the development of other safer routes for SIT. Especially in paediatrics, where needle phobia is more of an issue, SLIT was announced to be a useful and safe alternative. In contrast to SCIT, no treatment-associated deaths have been observed with SLIT although there are rare reports of systemic reactions during SLIT [45]. Post-marketing reports suggest that the rate of systemic reaction with grass pollen tablets, using the standard dosage, is 1 in 1000 patient [46]. Furthermore, it appeared that one of the major risks for a systemic reaction is moderate to severe asthma, especially when it was observed as a side-effect during previous SCIT treatment. This has led to the conclusion that SLIT will not be an alternative for SCIT when the latter has induced a systemic reaction.

The major side-effects associated with SLIT are the local reactions in the oral mucosa. In a phase I study with children it was shown that these local reactions included oral pruritus, throat irritation, mouth oedema, ear-pruritus as a projection of mouth itching, swollen lips, abdominal pain and cough [17]. Under these study conditions, up to 60% of the children experienced these reactions. During the phase III studies which systematically documented side-effects, they were observed in similar frequency as for adults [14, 16]. These observations have led the regulatory authorities and allergy societies to recommend in their guidelines that the first dosage should

still be given under medical supervision. To improve concordance, especially as the allergens normally have to be given daily, doctors are requested to explain the principle of the treatment and the concomitant risks thoroughly to the parents, recommend the application at the same time of day and prescribe only a restricted number of dosages in order to see the patients regularly during the treatment. Although SLIT seems to be safer than SCIT, it has yet not been proven that this is actually true when SCIT is used by experienced specialists. Furthermore, the lack of head to head studies in children comparing SCIT vs. SLIT, the recommendation for SLIT for children in the guidelines, at least in Germany, is restricted to those preparations which have been definitely shown to be effective in a reasonably powered child population and to the situation when SCIT cannot be used.

Prevention of polysensitization and asthma by specific immunotherapy

One of the most important reasons to start immunotherapy with allergens in childhood is the observations that it may prevent the development of asthma in children with AR and prevent the development of sensitization to additional allergens. It has been demonstrated that AR is an independent risk factor for subsequent development of asthma [47, 48]. Childhood AR may also predict the incidence of asthma in later age groups [49]. Additionally, anatomical analysis implies a continuous mucosa from upper to lower airways and immunology provides a close communication between both regions via bone marrow-derived cellular response [50]. These theoretical considerations have led to the one-airway hypothesis when talking about AR and asthma. Consequently, one might expect a secondary effect on the development of asthma in children with AR and treatment by immunotherapy. As a confirmation of this, in a retrospective analysis, children with AR who were treated by SIT were significantly less likely to be given an asthma diagnosis [51]. A randomized, open-controlled study in children with grass pollen extracts given as SLIT has also found a significant reduction of asthma diagnosis in the treatment group with an odds ratio of 3.8 [36]. Similar effects were seen in another open, controlled and randomized study using SLIT in addition to drug therapy [52]. Furthermore, the PAT study demonstrated a similar effect using SCIT with grass pollen extract in a prospective, open-controlled design after 3 years of treatment [26]. This reduction of asthma appeared to be a long-term effect since it remained unchanged for further 7 years after the end of SCIT [53]. Another aspect confirming the preventive effect of SIT comes from data indicating that immunotherapy is accompanied by the

development of less sensitization towards novel allergens and polysensitization [54]. Matricardi demonstrated early and strong sensitization to be a risk factor for later development of AR and asthma. In contrast, early weak mono-sensitization frequently disappears before the age of 5 years [55]. Interestingly, Gould and Sutton describe a mechanism by which the process of polysensitization may be mediated via the low-affinity IgE-receptor linked antigen presentation of B cells which can lead to epitope spreading not only in the same but also in different allergens [56]. It is still unknown what would trigger such a spreading of epitopes but it is tempting to speculate that SIT would be able to interact with this mechanism.

Although the preventive argument for the indication of SCIT in children with AR is frequently discussed, there are still scientific reservations due to the design of the studies providing the evidence for this hypothesis. A prospective, double-blind, placebo-controlled European study has recently been started using the incidence of asthma as the primary end-point after 3 years of treatment with a grass pollen tablet for SLIT which was demonstrated to be effective in adults and children. This well powered study has also included a further 2 years observation phase after cessation of therapy. Results will be expected at the end of the year 2015.

Summary

SIT as practiced since hundred years in Western Europe and the USA is an established treatment option for certain patients with allergic disease, whether children or adults. Although the clinical evidence in children for the traditional subcutaneous SIT and the more modern sublingual SIT is still debatable, recent data including sufficiently powered randomized controlled trials and reliable meta analyses indicate that especially for inhalant allergens such as pollen and mites as well as venom, SIT has its defined indication for treatment of AR and bronchial asthma. Further high quality clinical studies are needed in the paediatric population in order to understand whether SCIT and SLIT have equivalent efficacy and whether both prevent asthma in children with AR only. Risk factors for the occurrence of side-effects limiting the application of immunotherapy should be identified and measures should be developed to improve compliance to immunotherapy by the patients in order to increase efficacy. Additionally, it would be very helpful to have reliable diagnostic markers to identify those children who would benefit most from SIT for the improvement of symptoms and the secondary prevention of asthma.

References

- 1 Bousquet J. Current status of allergen immunotherapy (hyposensitization): memorandum from a WHO/IUIS Meeting. *Bull World Health Organ* 1989; **67**:262–7.
- 2 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.
- 3 Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 2008; **19**:110–24.
- 4 Schlaud M, Atzpodien K, Wulf AT, Thamm M. Prevalence of allergic diseases and sensitisations – results from the German Health Survey for Children and Adolescents (KiGGS). *Allergy* 2007; **62**:86.
- 5 Schlaud M, Atzpodien K, Thierfelder W. Allergische Erkrankungen; Ergebnisse aus dem Kinder- und Jugendgesundheitsurvey (KiGGS). *Bundesgesundheitsblatt* 2010; **50**:701–10.
- 6 Linneberg A, Nielsen NH, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2001; **57**:1048–52.
- 7 Visiongain. The World Allergy Market, 2006–2011. A Visiongain Report, Visiongain, Rx-OTC-Rush, 1–116. 2011, Visiongain.
- 8 Blumchen K, Ulbricht H, Staden U *et al.* Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010; **126**:83–91.
- 9 Miceli Sopo S, Onesimo R, Giorgio V, Fundaro C. Specific oral tolerance induction (SOTI) in pediatric age: clinical research or just routine practice? *Pediatr Allergy Immunol* 2010; **21**:e446–9.
- 10 Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases – a WHO position paper. *J Allergy Clin Immunol* 1998; **102**:558–62.
- 11 Canonica GW, Bousquet J, Casale TB *et al.* Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009; **64**:1–59.
- 12 Kleine-Tebbe J, Bufer A, Ebner C *et al.* Specific immunotherapy (hyposensitization) for IgE-mediated allergic diseases. *Allergologie* 2010; **33**:3.
- 13 Drachenberg KJ, Wheeler AWSUP, Horak F. Short-course specific immunotherapy (SIT) adjuvanted by monophosphoryl lipid A (MPL). A multi-centre, double-blind, placebo-controlled study. *Allergy* 2000; **55**:142 (abstract).
- 14 Bufer A, Eberle P, Franke-Beckmann E *et al.* Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; **123**:167–73.
- 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**:160–6.
- 16 Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2007; **119**:780–9.
- 17 Ibanez MD, Kaiser F, Knecht R *et al.* Safety of specific sublingual immunotherapy with SQ standardized grass allergen tablets in children. *Pediatr Allergy Immunol* 2007; **18**:516–22.
- 18 Mosges R, Graute V, Christ H, Sieber HJ, Wahn U, Niggemann B. Safety of ultrarush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy. *Pediatr Allergy Immunol* 2010; **21**:1135–8.
- 19 Kaul S, Englert L, May S, Vieths S. Regulatory aspects of specific immunotherapy in Europe. *Curr Opin Allergy Clin Immunol* 2010; **10**:594–602.
- 20 Roder E, Berger MY, de Groot H, Van Wijk RG. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review. *Pediatr Allergy Immunol* 2008; **19**:197–207.
- 21 Sanders S. Treatment of seasonal hay fever and asthma in children. *Practitioner* 1996; **196**:811–15.
- 22 Fontana VJ, Holt LE, Mainland D. Effectiveness of hyposensitization therapy in ragweed hay-fever in children. *JAMA* 1966; **195**:985–92.
- 23 Weisnagel J. New hyposensitizing agent in the treatment of ragweed hay-fever in children – MRTA (modified ragweed tyrosine absorbate). *Union Med Canada* 1979; **108**:685–90.
- 24 Dreborg S, Agrell B, Foucard T, Kjellman NIM, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation. 1. clinical-results. *Allergy* 1986; **41**:131–40.
- 25 Urbanek R, Behle M, Kuhn W. Die Problematik der Hausstaubmilbenallergie. *Pädiatr Pädol* 1991; **26**:25–30.
- 26 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.
- 27 Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007.
- 28 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.
- 29 Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2010; **126**:942–49.
- 30 Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2003; **2**:CD002893.
- 31 Penagos M, Compalati E, Tarantini F *et al.* Efficacy of sublingual immunotherapy 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**:141–8.
- 32 Radulovic M, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010; **12**:CD002893.
- 33 Bufer A, Ziegler-Kirbach E, Stoeckmann E *et al.* Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004; **59**:498–504.
- 34 Rolinck-Werninghaus C, Wolf H, Liebke C *et al.* A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004; **59**:1285–93.
- 35 Nieto A, Mazon A, Parnies R, Bruno L, Navarro M, Montanes A. Sublingual im-

- munotherapy for allergic respiratory diseases: an evaluation of meta-analyses. *J Allergy Clin Immunol* 2009; 124:157–61.
- 36 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.
 - 37 Dahl R, Kapp A, Colombo G *et al.* Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 118:434–40.
 - 38 Halken S, Agertoft L, Seidenberg J *et al.* Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol* 2010; 21:970–6.
 - 39 Durham S, Dahl R, Kapp A *et al.* Sustained, disease-modifying effect of grass allergen tablet immunotherapy 1 year after completion of treatment. *Allergy* 2009; 64:146.
 - 40 Durham SR, Emminger W, Kapp A *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.
 - 41 Bufe A, Henmar H, Gronager PM, Durham SR. Sublingual immunotherapy with fast-dissolving grass tablets induces comparable IgG4 antibody and IgE-blocking responses in children and adults. *J Allergy Clin Immunol* 2009; 123:S75.
 - 42 Holt PG. Fetal and neonatal immunology and the mucosal immune system. In Cantani A, ed. *Pediatric Allergy, Asthma and Immunology*. Berlin: Springer Verlag GmbH, 2007; 221–68.
 - 43 Winther L, Arnved J, Malling HJ, Nolte H, Mosbech H. Side-effects of allergen-specific immunotherapy. A prospective multi-centre study. *Clin Exp Allergy* 2006; 36:254–60.
 - 44 Lüderitz-Püchel U. Neubewertung des Risikos von Test- und Therapieallergenen. Eine Analyse der UAW-meldungen von 1991 bis 2000. *Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz* 2003; 44:709–18.
 - 45 de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009; 64:963–4.
 - 46 ALK-Abello. GRAZAX 75,000 SQ-T oral lyophilisate – summary of product characteristics. EMC. 8–11-2010. Data-pharm Communications Ltd. Available at http://www.medicines.org.uk/emc/medicine/19565/SPC/GRAZAX_75,000_SQ-T_oral_lyophilisate/
 - 47 Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol* 1999; 103:54–9.
 - 48 Halpern MT, Schmier JK, Richner R, Guo CF, Togias A. Allergic rhinitis: a potential cause of increased asthma medication use, costs, and morbidity. *J Asthma* 2004; 41:117–26.
 - 49 Burgess JA, Walters EH, Byrnes GB *et al.* Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol* 2007; 120:863–9.
 - 50 Bousquet J, Khaltaev N, Cruz AA *et al.* Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63:8–160.
 - 51 Polosa R. A clinical-based retrospective cohort study of incidence asthma in adults with allergic rhinitis: importance of cigarette smoking. *J Allergy Clin Immunol* 2006; 117:S216.
 - 52 Marogna M, Tomassetti D, Bernasconi A *et al.* Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008; 101: 206–11.
 - 53 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.
 - 54 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, placebo-controlled study. *Allergy* 2000; 55: 842–9.
 - 55 Matricardi PM, Bockelbrink A, Keil T *et al.* Dynamic evolution of serum immunoglobulin E to airborne allergens throughout childhood: results from the Multi-Centre Allergy Study birth cohort. *Clin Exp Allergy* 2009; 39:1551–7.
 - 56 Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nature Rev Immunol* 2008; 8:205–17.