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Abstract: Subcutaneous immunotherapy (SCIT) is still questioned as a safe and efficacious way of treating allergic asthma in children. In a Cochrane review published in 2010 it was, however, concluded that SCIT has significant and beneficial effects on symptoms and medication use in both children and adults with mostly mild asthma. Only a few studies have been performed to specifically study if SCIT in children with moderate asthma reduces the need for inhaled corticosteroids. There are conflicting results that illustrate the problem of the heterogeneity of the asthma disease and the fact that allergies may play different roles on the severity and symptoms of the disease. Furthermore, children with severe allergic asthma are often sensitized to multiple allergens, which makes SCIT both complicated and less safe to administer. On the other hand, if the child suffers from asthmatic symptoms despite adherence to pharmacotherapy, omalizumab or a combination of omalizumab and allergen immunotherapy might be useful. There is a need for more studies on this combination before it can be considered as an additional therapy in children with asthma and severe allergies. Sublingual immunotherapy (SLIT) has also been shown to improve asthma symptoms and medication use. SLIT is safe although its efficacy compared with SCIT has been studied very little. Another approach is to try to prevent asthma by treating children with SCIT for allergic rhinoconjunctivitis before asthma has developed. The most attractive prospect, however, is to find ways of preventing asthma by vaccination against the most common viruses, particularly rhinovirus. There is evidence that there are children at high risk of developing asthma in whom a viral infection can also enhance the risk of allergen sensitization. So far this vaccination has not been achievable although research is in progress.

Keywords: allergy, asthma, childhood, immunotherapy

Introduction

The majority of schoolchildren with asthma are allergic to airborne allergens and allergy is a common trigger of asthma symptoms [Arbes *et al.* 2007; Covar *et al.* 2010]. Nevertheless, subcutaneous immunotherapy (SCIT) is still questioned as a safe and efficacious way of treating allergic asthma in children. In a GA2LEN report, the Consolidated Standards Of Reporting Trials (CONSORT) recommendations were used to evaluate the results of previously performed immunotherapy studies. This evaluation concluded that very few, if any, immunotherapy studies met all the criteria of the CONSORT statement [Bousquet *et al.* 2011]. These

recommendations state that dropouts should be reported, a sensitivity analysis should be performed if more than 25% of the subjects drop out, intention-to-treat analysis should be carried out, patients with efficacy data should not be excluded (e.g. due to lack of adherence), there should be no per patient analysis and blinding procedures must be adequate [Bousquet *et al.* 2011]. On the other hand, a Cochrane analysis published in 2010 concluded that immunotherapy reduces asthma symptoms and the use of medications, improves bronchial hyperreactivity (BHR), and that the trial results analysed could be compared with the effects of inhaled corticosteroids (ICS) [Abramson *et al.* 2010].

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Diagnostic procedures and allergy confirmation

Before considering immunotherapy, the allergens responsible for causing asthma symptoms have to be confirmed [Hankin and Lockey, 2011]. Although allergy is a common cause of these symptoms and often of exacerbations, it is not always clear the role a specific allergen plays in the severity of the disease [Platts-Mills and Woodfolk, 2011]. This is particularly obvious when the relationship between exposure and symptoms is not clear. For example, when patients are allergic to dust mites it is possible to measure dust mite levels in the home, while measuring exposure to spore levels in mould allergy is more complicated. In pollen allergy, the relationship between exposure and symptoms is easy to assess using pollen count reports. For patients allergic to animal dander, the exposure to dander present on clothes, hair or on surfaces in the home, school or other public places constitutes an invisible source of allergen [Almqvist *et al.* 1999]. Under these circumstances it can be difficult to evaluate the impact of allergy on a child's symptoms.

These examples highlight the importance of performing a careful, thorough diagnosis of allergy before the decision to initiate immunotherapy is made [Zuberbier *et al.* 2010]. Furthermore, allergic sensitization is not always a relevant cause of symptoms. In a birch pollen exposure study [Kihlström *et al.* 2002], children born before high and low birch pollen seasons were examined at 5 years of age. The children born before the high pollen season in 1993 had more than double the risk of being sensitized to birch than the children born before the low pollen season in 1994. When asked about symptoms of pollen allergy only half of the children sensitized to birch confirmed that they had suffered symptoms during the previous season. The questions raised by this response were whether in fact the sensitization was not important or whether symptoms would appear later in life. A similar finding was reported in a Swedish birth cohort study; cat sensitization was demonstrated in 4-year-old children without symptoms of cat allergy [Saarne *et al.* 2010]. If the sensitization was a sign of a developing symptomatic allergy, would this then indicate that allergic symptoms later in life could be prevented if immunotherapy was initiated at this stage? To date this question remains unanswered as no preventive allergy immunotherapy studies have been initiated before a child has developed symptoms of rhinitis in order to prevent asthma.

For seasonal pollen allergy there is usually no need to confirm a relationship between sensitization, exposure and symptoms by any other means than taking a history and an analysis of allergen-specific blood IgE or a skin-prick test [Zuberbier *et al.* 2010]. In animal dander allergy, there is also a clear relationship between exposure and allergic symptoms [Arvidsson *et al.* 2007], yet this may not always be the case. On the other hand, as mentioned above, a 'disguised' exposure to environmental dander in the absence of an obvious animal presence can also cause symptoms [Almqvist *et al.* 2001]. As mentioned above, exposures to dust mites and sometimes moulds are amongst the most 'invisible' making it difficult to evaluate the impact of the specific allergy on the symptoms presented [Matsui *et al.* 2010]. While *in vitro* tests or skin tests are adequate for confirming pollen and animal dander allergy, it may be necessary to perform allergen provocation tests in the eyes and/or the nose to confirm a dust-mite allergy [de Blay, 2011; Fernandez *et al.* 2011]. The possibility of applying improved and detailed diagnostic procedures by allergen component analysis will further refine the precision of allergy diagnosis [Sastre, 2010].

Criteria for the commencement of immunotherapy

A correct diagnosis before commencing immunotherapy treatment is mandatory. More information on the relevant procedures can be found in the position paper published as a GA2LEN/European Academy of Allergy and Clinical Immunology pocket guide on allergen-specific immunotherapy for allergic rhinitis and asthma [Zuberbier *et al.* 2010]. Even in the presence of such guidelines, the fundamental question is still whether or not there is a role for immunotherapy in managing childhood asthma. There are also contraindications to be considered such as asthma with daily symptoms and/or poor lung function (forced expiratory volume in 1 s < 70%), autoimmune or malignant diseases and current therapy with beta-blockers [Zuberbier *et al.* 2010].

More specifically we need to know whether immunotherapy can fulfil the following four criteria.

- (1) prevent asthma in atopic children;
- (2) prevent the deterioration of asthma in patients with mild asthma and allergic rhinitis;

- (3) reduce the need for ICS in children with moderate persistent asthma;
- (4) provide safe and effective treatment in combination with anti-IgE in children with severe allergic asthma.

Immunotherapy for asthma prevention in atopic children

There are no placebo-controlled studies on SCIT and the prevention of asthma. The best known study, the Preventive Asthma Trial (PAT), was an open, randomized study comparing SCIT for pollen allergy with traditional pharmacotherapy in children with pollen allergic rhinitis and no symptoms of asthma. After 3 years of therapy, twice as many children in the pharmacotherapy group had asthma symptoms compared with the SCIT group. The assessment of BHR by methacholine challenge supported this result as there was a significant difference between the groups [Möller *et al.* 2002]. The children were followed for 7 years after cessation of therapy and at the 10-year evaluation an effect on symptoms remained, but the difference in methacholine reactivity had disappeared [Jacobsen *et al.* 2007]. Two open studies, both with the same intention, to prevent asthma using sublingual immunotherapy (SLIT) have been published. One study was performed on 113 grass allergic children [Novembre *et al.* 2004], and another on 216 children with rhinitis and intermittent asthma [Marogna *et al.* 2008]. The first demonstrated an increased risk of new asthma in the control group, and the second demonstrated a decreased risk of persistent asthma in the SLIT group. In a fourth placebo-controlled study of children and young adults with rhinitis and increased BHR, a decrease in BHR and preventive effects on asthma symptoms were found in the actively treated group [Grembale *et al.* 2000]. Taken together the evidence, albeit relatively weak, indicates that immunotherapy can have a preventive effect on the development of asthma symptoms in subjects with rhinitis, with or without BHR. A randomized, 3 year, placebo-controlled trial is currently underway to investigate the use of grass tablets in children with grass-allergic rhinoconjunctivitis [Valovirta, 2011].

Immunotherapy for mild asthma and allergic rhinitis to improve and/or prevent deterioration of asthma

The majority of immunotherapy studies in children (and adults) with asthma have been

performed in those with mild asthma, usually combined with rhinitis. These are the studies that have provided the evidence supporting the efficacy of immunotherapy in subjects with allergic asthma [Abramson *et al.* 2003, 2010]. Most of the studies have been performed using single allergens; the most predominant perennial allergen being dust mites, and the dominant seasonal allergens being birch, grass and ragweed. Numerous studies have been performed and published over the 100 years since immunotherapy was first practised [Ring and Gutermuth, 2011]. Together with the development of standardized extracts and increasing knowledge of the mechanisms underlying this treatment [Akkoc *et al.* 2011], studies have been performed to investigate the efficacy of new extracts, beneficial or improved effects of new adjuvants to extracts [Ring and Gutermuth, 2011], different dosing schedules [Demoly and Calderon, 2011; Cox *et al.* 2011], dose levels of major allergens [Calderon *et al.* 2011], and safety issues [Iglesias-Cadarso and Hernandez-Weigand, 2011]. Few studies have compared immunotherapy to topical corticosteroids in mild asthma. Last but not least, some studies have carried out long-term follow ups to investigate how long the treatment effects last [Naclerio *et al.* 1997; Hedlin *et al.* 1995; Eifan *et al.* 2011].

The best evidence demonstrating efficacy of immunotherapy in children with asthma has resulted from treatment of children allergic to pollen and dust mites. Although many studies have been performed in schoolchildren and adults, few have included schoolchildren only, or preschool children, the latter having been included in very few of the randomized and placebo-controlled trials, if any [Abramson *et al.* 2003, 2010].

One example of a well-designed, placebo-controlled study of SCIT in children is a grass pollen study from Southampton, UK. This was a small study including fewer than 20 children in each group, but nevertheless, still showing significant effects of immunotherapy on seasonal grass allergy in asthmatic children [Roberts *et al.* 2006]. Other studies of dust-mite immunotherapy in children with asthma have seldom been placebo controlled. A 3-year controlled trial in children monoallergic to dust mite, involved the completion of symptom diaries during a 1-year run-in period, as well as lung function and methacholine tests. This study reported a significant decrease in

BHR and the number of days requiring oral corticosteroid treatment for asthma exacerbations [Pifferi *et al.* 2002]. A similar result was reported in another dust-mite study including the evaluation of BHR as measured by cold-dry air challenge [Gruber *et al.* 1999]. However, the improvement shown in this study was only achieved after 2 years of immunotherapy. In the early 1980s, we performed a double-blind, placebo-controlled study of children and adults with cat or dog dander allergy, and mild to moderate asthma. The treatment consisted of standardized extracts and the patients carried out bronchial allergen and histamine challenges [Hedlin *et al.* 1991]. The effect of SCIT was very good and mixed, with the cat extract having a beneficial effect both on allergen sensitivity and BHR, while the dog extract had only some effect on allergen sensitivity but no effect on BHR. The 5-year follow-up study demonstrated a remaining effect on BHR. Sensitivity to the bronchial challenge with cat extract was greater at this timepoint, although still lower than before therapy. Interestingly, the patients did not report increased symptoms on exposure to the relevant animal despite the allergen challenge results [Hedlin *et al.* 1995]. Today we know more about the remaining effect on the late phase reaction through studies performed in adults with grass pollen allergy [Durham, 2011]. We also know more about possible sustained effects due to allergen-specific blocking IgG4 antibodies [James *et al.* 2011]. Finally, a recent study of treatment with *Alternaria* extracts in children showed convincing clinical effects, reducing symptoms of both rhinoconjunctivitis and asthma [Kuna, 2011].

Immunotherapy to improve moderate persistent asthma and to reduce the need for ICS

Surprisingly few studies have been performed in children with moderate asthma in need of daily anti-inflammatory therapy. Long-term studies like the Childhood Asthma Management Program (CAMP) have shown that pharmacotherapy with ICS does not affect the long-term natural history of asthma [Strunk *et al.* 2009]. The CAMP study was designed to evaluate the effect of budesonide compared with nedocromil and placebo during a 5-year treatment period. The beneficial effect of ICS on symptoms of asthma was convincing, compared with both nedocromil and placebo after the 5-year study period [CAMP, 2000]. A long-term follow-up study has shown, however,

that this effect does not remain, and that symptoms recur over a period of 4 years if therapy is stopped. Only about 5% of the children had no symptoms of asthma during the year prior to the follow up. Furthermore, there were no significant differences between the three groups in the long-term follow up, and thus, no indication of a sustained effect in a 5-year ICS treatment in children with moderately severe asthma [Strunk *et al.* 2009]. The lack of long-term benefit with ICS therapy could increase our interest in SCIT due to the question as to whether SCIT may alter the severity of asthma and, if this was possible, would the attenuation in severity be sustainable.

SCIT with single allergens. There are few studies in children concerning SCIT and the reduction of pharmacotherapy, particularly in children with perennial allergy. In seasonal allergy to pollen, we know more about the effect of SCIT on the need for antihistamines rather than the need for topical corticosteroids [Calderon *et al.* 2007]. A comparable effect of SCIT and nasal corticosteroids has been shown in adults [Rak *et al.* 2001]. Two studies of dust-mite therapy, one using SCIT and the other using SLIT, aimed to decrease the dose of ICS [Maestrelli, 2004; Pham-Thi *et al.* 2007], but neither could demonstrate any significant reduction in the need for ICS. A recent study, however, did report a steroid-sparing effect of SCIT in children with asthma and dust-mite allergy [Zielen *et al.* 2010]. The study was randomized but not placebo controlled. Another study is currently being conducted with the aim of reducing the need for ICS in dust-mite allergy and asthma [Mosbech, 2011]. This study is placebo controlled and should strengthen the data currently available.

SCIT with multiple allergens. Few studies have been carried out in children with both seasonal and perennial allergies. One study is particularly noteworthy [Adkinson *et al.* 1997]. Children with multiple allergies were included and randomized after optimization of their pharmacotherapy to either SCIT with a maximum of six extracts in a mixture, allowing one injection at each visit, or a placebo injection over a period of 2 years. The children were monitored by daily peak flows, regular visits and re-evaluations of the need for pharmacotherapy according to an algorithm, and also by repeated methacholine challenges. One interesting finding was that both groups of children improved during the study time. There was, however, no significant difference between

the groups in any of the relevant parameters, and more specifically, there was no difference in the need for ICS in symptom control.

The finding of an improvement in both groups points to the fact that careful and regular check ups, and adherence to pharmacotherapy, does make a difference and is in itself an important part of the care of children with asthma. This could also be one of the conclusions of the results of the CAMP study [CAMP, 2000]. Referring to the failure of the SCIT therapy to reduce the need for ICS, there are some aspects of this study that could partly explain these findings. The children were multiallergic; many of them were also allergic to animal dander and cockroaches, which were not included in the therapy. In most cases, avoidance of these allergens is not possible, thus most children in the study continued to be exposed to the offending allergens throughout the study period.

Another possible explanation could be that the mix of allergens used may have contributed to a degradation of the allergen content, although the quality of the single allergens was standardized. The risk of mould allergens degrading other allergens in a mixture has been discussed and it was recommended that dust-mite extracts should not be mixed with extracts of fungi [Esch, 2008]. In one of our own studies, we randomized children with cat and pollen allergies and asthma to either receive placebo or active cat extract in parallel with one pollen extract for a 3-year treatment period [Hedlin *et al.* 1999]. Our aim was to find out if cat SCIT combined with a relevant pollen extract would decrease the need for ICS and BHR in a group of children with moderate asthma requiring daily ICS. We could confirm, as in our earlier study of cat SCIT, that this treatment was very effective in the treatment of cat allergy; more than half of the children receiving cat extract did not react at all to a bronchial allergen challenge after 3 years of therapy. Interestingly, there was a decrease in the sensitivity towards cat even in the placebo group. A possible explanation could be that, as in the study by Adkinson and colleagues, asthma improved due to the continued regular visits encouraging adherence to the pharmacotherapy [Adkinson *et al.* 1997]. Another possible explanation could be that the pollen SCIT decreased the seasonal increase in symptoms and BHR, which contributed to the decrease in sensitivity to bronchial allergen. A disappointing finding, however, was that the need for ICS to control

symptoms, according to the algorithm devised for this study, did not change significantly [Hedlin, 1999].

Finally, one more study could be mentioned in this context, in which montelukast was added to SCIT in a randomized, placebo-controlled study. The aim of the study was to find out whether montelukast would provide additional benefit in combination with SCIT. The results, however, pointed in the opposite direction in that montelukast either had no beneficial effect on the response to SCIT or somehow contributed to a poorer response [Majak *et al.* 2010].

Dosing schedules for SCIT. The stepping up of the dose phase of SCIT treatment is still being discussed and different up dosing regimens are used. There are rush up dosing schedules, cluster regimens [Jung, 2011], and the conventional one injection per week regimen. The advantages and disadvantages of different immunotherapy schedules have been discussed as well as the beneficial effects of pretreatment with antihistamine [Muller *et al.* 2008]. A cat allergen study was designed to establish the optimal dose required to have an effect on skin test, nasal challenge and allergen specific IgG4 levels. The conclusion of this study was that after 5 weeks of treatment, the combined results of these three parameters could predict the result of 1 year of treatment as well as the optimal dose [Nanda *et al.* 2004]. A similar study has also been performed with dog-dander extract [Lent *et al.* 2006].

In one review [Cox *et al.* 2011], the risk of systemic side effects were considered and the highest risk was reported when a rush regimen was used. There are some examples of cluster regimens not causing any systemic effects after pretreatment. However, none of the schedules are without risk of systemic side effects, which is an important reminder of the risk that is always present and therefore requires special attention, the implementation of safety measures and standardized procedures. The guidelines available serve an important role in providing standards for the use of immunotherapy [Jung, 2011; Cox *et al.* 2011].

SLIT for asthma. Sublingual immunotherapy for asthma in children has been the subject of a couple of meta-analyses [Penagos *et al.* 2008; Nieto *et al.* 2009]. The conclusion of the first analysis was that SLIT with standardized extracts reduces both symptom score and rescue medication use in

children with allergic asthma, compared with placebo. Out of 79 published studies, nine were considered adequate by being randomized, double-blind and placebo-controlled in children. Six of the studies were performed using dust-mite extracts and three included pollen extracts. One interesting finding was that there was a large variation in the cumulative dose of dust mite administered, ranging from 0.25 mg to 12 mg Der p. This is an issue that has been discussed, and has caused some concern, in that there are still few dose-response studies that have confirmed the standard doses that should be used for SLIT. In their review, Nieto and colleagues address this issue, as well as others, in an evaluation of two meta-analyses [Nieto *et al.* 2009]. They combined the results of the two meta-analyses [Penagos *et al.* 2008; Wilson *et al.* 2005]. Their conclusion is that current evidence is not strong enough to support the routine use of SLIT as the conclusions of studies in children are inconsistent and contain discrepancies.

In one interesting recent study, SLIT in children allergic to dust mite was compared with SCIT and pharmacotherapy [Eifan *et al.* 2010]. Symptom evaluation using the visual analogue scale demonstrated a lack of effect of pharmacotherapy, a fairly small and varied effect of SLIT, and a significant and increasing effect of SCIT during a 12-month treatment period. These results indicate a need for more placebo-controlled studies to establish adequate SLIT dosages for the treatment of asthma in children, and more studies comparing SLIT and SCIT.

Dose and dosing are still major issues for SLIT. The importance of using an adequate dose to achieve a desired response has been studied in both SCIT and SLIT [Calderon *et al.* 2011].

Immunotherapy combined with anti-IgE: safety and efficacy in children with severe allergic asthma

Few studies have addressed this question in children. One of the paediatric studies was performed in polysensitized children with seasonal rhinitis and included children with birch or grass allergy. [Kuerh *et al.* 2002]. Results showed that the combination of omalizumab and pollen SCIT had superior effects on symptom load in both the birch and grass allergic children. Other studies performed in groups of children and adults have shown similar results. Another study also showed

a superior effect of SCIT when combined with omalizumab, particularly on asthma control [Kopp *et al.* 2009]. In this study, 23% of subjects were children with both asthma and seasonal rhinoconjunctivitis. Pretreatment with omalizumab in patients with severe multiallergic asthma was the subject of yet another study of combined therapy, although here omalizumab treatment only overlapped at the start of immunotherapy in symptomatic patients with asthma. The risk of systemic side effects was reduced, although eight severe systemic reactions still occurred in the group pretreated with omalizumab, compared with 26 in the group pretreated with placebo [Massanari *et al.* 2010]. In this context, the use of omalizumab in the absence of SCIT may be mentioned, as there have now been some successful, controlled studies in children with allergic asthma. The main outcome observed has been on reducing the risk of exacerbations [Lanier *et al.* 2009; Busse *et al.* 2011]. However, to date, no studies have shown a convincing long-lasting effect of omalizumab after cessation of therapy. As mentioned before, one controlled and two open studies have demonstrated long-lasting effects of SCIT on symptoms [Frew, 2010].

Future possibilities

Has this review of SCIT and SLIT studies in children with allergic asthma provided answers to the four criteria mentioned? Can immunotherapy prevent asthma in atopic children? The answer is, possibly, but evidence obtained from placebo-controlled trials is still needed, particularly in view of the fact that the result of the long-term PAT study varied in the different study centres. Nevertheless, several studies have still demonstrated an attenuation of BHR, which could indicate a preventive effect on asthma.

Can immunotherapy for mild asthma and allergic rhinitis prevent deterioration and improve symptoms of asthma? Here the answer is yes. This has been the subject of the majority of studies performed in patients with asthma, both in adults and children, and it is supported by the Cochrane reports on the subject.

Can immunotherapy moderate multiallergic-persistent asthma and reduce the need for ICS and/or improve asthma severity? The answer is still unknown. Studies on dust-mite and cat SCIT have shown convincing effects on specific allergies, but the overall effect on asthma severity

has not been convincing. Few studies have been designed to address this question, and as Nelson points out in a review on multiallergen immunotherapy for allergic rhinitis and asthma, more studies are needed, particularly with more than two allergen extracts and using sublingual administration [Nelson, 2009].

If immunotherapy is combined with anti-IgE, can it be safe and effective in children with severe allergic asthma? The answer is that we do not know as, so far, no studies have been performed in children with severe allergies and asthma, combining omalizumab and SCIT or SLIT. In light of the short-lasting effects of omalizumab treatment, it may be beneficial to combine omalizumab and immunotherapy, both for short-term and long-term effects in children who currently require better treatment options for persistent allergic asthma.

As knowledge increases on the interaction between innate antiviral and atopic immune inflammatory pathways in childhood asthma, combining vaccines for allergic and infectious disease may be a way, in the future, to prevent asthma and allergies early in life. The generation of such a vaccine, a combination vaccine for grass pollen allergy and rhinovirus, has recently been reported [Subrata *et al.* 2009; Edlmayr *et al.* 2011]. Furthermore, since the genetic code of the most important allergens has been deciphered and the first immunotherapy studies with recombinant allergens have shown promising results [Valenta *et al.* 2011a, b], a new era with personalized vaccines may become possible. Finally, the novel epicutaneous route and the intralymphatic nodular administration route are exciting new modes for allergen delivery [Senti *et al.* 2008, 2011]. Whether all these options will be part of the future treatment of childhood asthma remains to be elucidated.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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