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REVIEW ARTICLE

Immunotherapy in Allergic Rhinitis

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Abstract:
Allergic rhinitis is an immunologic disorder that develops in individuals who have produced allergen-specific immunoglobulin E in response to environmental exposures (most commonly to pollens, animal dander, insect debris, and molds). For patients with a severe allergy that is not responsive to environmental controls and pharmacotherapy or for those who do not wish to use medication for a lifetime, immunotherapy may be offered. Specific immunotherapy as practiced since hundred years in Western Europe and the USA. Different routes for specific immunotherapy have been evaluated, such as the subcutaneous, sublingual, oral, nasal, bronchial, and intra-lymphatic, the first 2 of these routes being the most commonly used today in clinical practice. In this article, subcutaneous and sublingual immunotherapy in allergic rhinitis is reviewed.

Keywords: *Immunotherapy, Allergic Rhinitis*
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Introduction

Allergic rhinitis (AR) is a very common disease with a high and still increasing world prevalence. The International Study of Asthma and Allergies in Childhood (ISAAC) demonstrated in the 1990s 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%) (1). 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 (2). About 40–60% of children with AR suffer from concomitant asthma symptoms (3).
While allergic rhinitis is not a life-threatening condition, it can impair quality of life and influence the work and school performance. Also it increases the health care costs by direct and indirect ways. AR causes an important medical and social burden which further increases when the disease is associated with allergic asthma (3,4). In fact, the concurrence of AR and asthma requires more doctor visits and more drugs and worsens patients quality of life and increases the risk of asthma exacerbations (3). Because of all these reasons, its diagnosis and treatment is important.

Treatment should start with avoidance of allergens and environmental controls. In almost all cases, however, pharmacotherapy is needed because the patient is either unwilling or unable to avoid allergens and to control the occasional exacerbations of symptoms. For patients with a severe allergy that is not responsive to

environmental controls and pharmacotherapy or for those who do not wish to use medication for a lifetime, immunotherapy may be offered (5). In this article, immunotherapy treatment of allergic rhinitis is reviewed .

Spesific ımmunotherapy (SIT) as practiced since hundred years in Western Europe and the USA. Allergen- spesific immunotherapy involves the administrration of specific allergens to achieve a hyposensitization such that the symptoms occuring during the natural exposure to the allergen are reduced (5,6). In particular, it is used for allergic disorders such as seasonal and perennial allergic rhinitis and allergic asthma (6). SIT is targeted at a large and variable range of allergens. The use of SIT as therapy for allergic respiratory diseases has been recognized in different international guidelines and by the World Health Organization (7,8,9). Different routes for SIT have been evaluated, such as the subcutaneous, sublingual, oral, nasal, bronchial, and intralymphatic, the first 2 of these routes being the most commonly used today in clinical practice (10).

Subcutaneous immunotherapy (SCIT) is stil the most commonly used route for the treatment of allergic rhinitis and allergic asthma in adults and children. Sublingual immunotherapy (SLIT) was introduced as an alternative to SCIT in the late 1970s. Allergen extracts for SLIT can be administered as drops or fast-dissolving tablets. At present, its prescription by allergists is becoming more frequent in several countries worldwide, mainly within Europe (11).

Subcutaneous injection immunotherapy (SCIT)

Immunotherapy was first developed at St Mary's Hospital London at the end of the 19th century, and many of the basic principles described by Noon and Freeman remain valid today (12,13). In 1911, Leonard Noon published in the Lancet a description of his treatment of patients suffering from grass pollen–induced hay fever. In keeping with immunologic thinking of the day, he hypothesized that these individuals were uniquely sensitive to a toxin contained in the grass pollen. And that by a series injections increasing amounts of grass pollen extract could induce protective antibodies against this toxin (12). In an era when there was no effective symptomatic treatment for respiratory allergies, the practice of subcutaneous injection immunotherapy spread rapidly, and was extended to a wide range of allergens and conditions. Subcutaneous immunotherapy has been successfully employed for the entire range of inhalant allergens, including pollens, animal danders, house dust mites, and fungi as well as for allergy to insect stings (14). Despite this extension of subcutaneous immunotherapy to other allergens and other allergic conditions, the basic approach, that of a series of graded increasing doses followed by a prolonged series of maintenance injections, has changed little over the course of the 100 years that it has been employed (14).

SIT is the practice of administering gradually increasing doses of the specific causative allergen to reduce the clinical reactivity of allergic subjects. This treatment has pivotal importance because of its ability to modify the natural history of the disease and to extend its effectiveness after treatment withdrawal, provided it is administered with sufficiently hgh doses and for an adequate duration (14,15). Subcutaneous immunotherapy has been the traditional technique of administration for decades (14).

As in adults, allergen extracts for subcutaneous application are prepared individually and distributed via the pharmacies or the companies directly. According to the European and national immunotherapy position papers and guidelines, best practical and longterm experience in children is observed with a 3 years treatment phase with or without co-seasonal reduction. Novel developments even suggest that only three to seven injections once a year are effective (16-18).

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 minutes (60 minutes 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 (19-21).

SIT has a different mechanism. This mechanism of action has been unique and different from any other pharmacological treatment in many respects. Firstly, SIT can modify the natural history of allergic disease, as confirmed in rigorously conducted trials (22,23). Secondly, SIT can prevent the onset of new sensitizations, as demonstrated clearly in children in several studies (24,25). Thirdly, SIT even maintains its clinical efficacy years after discontinuation (26,27).

Specific immunotherapy is the only treatment, able to modify the natural history of the allergic diseases. There are many clinical trials which show SIT to be an effective treatment in the management of allergic diseases, but its mechanism of action is still not clearly understood (27). Earlier studies showed changes in antibodies and it may be that SIT works through mechanisms that alter the ratio of "protective" IgG4 to "pro-allergenic" IgE. Other studies have shown a reduction in mast cells and eosinophils migration to nasal mucosa as well as a reduction in inflammatory mediator release including basophil histamine release. Recent studies have proposed that SIT works through inhibition of T-helper2 lymphocytes (Th2) which preferentially produce cytokines that promote allergic responses (27). High-dose allergen exposure during SIT results in both immune deviation of Th2 responses in favor of Th0/Th1 response and in the generation of IL-10 and TGF-beta producing CD4+CD25+ Treg cells. Secondarily stimulates the induction of T regulatory cells, secreting IL-10 or TGF-β, resulting in a global decrease in the secretion of Th2 (i.e.. IL-4, IL-5, IL-9 and IL-13) and Th1 cytokines (i.e., IFN-γ and IL-2), and in T-cell hyporesponsiveness (28-30) (Figure 1). A shift from a Th2 to a Th1 pattern of cytokine secretion in peripheral blood mononuclear cells is often demonstrated, although other studies do not reproduce this effect (30-32). A pure Th1 shift may actually be detrimental for airways and may lead to enhanced inflammation rather than to allergen-specific tolerance (33). Allergen-specific IgG4 enhancement occurs later in the course of SCIT, presumably in relation to the rise in IL-10 secreted by CD4+ regulatory T cells (29,31,34-36). Allergen-specific IgG1 and IgG4 antibodies have IgE-blocking capacities, and may compete with IgE for common B-cell epitopes on allergens or trap allergen prior to its binding to receptor-bound IgE (37-39). IgG1 and IgG4 may, thus, contribute to protection upon exposure, although this topic remains controversial. SIT surrogate markers of protection are still severely lacking. Allergen-specific IgEs slowly decrease over time, although they do not disappear in most cases (40). SCIT ultimately leads to the induction of T regulatory cells, an effect that is interesting when considered with the known imbalance in CD25+ T regulatory cells present in asthmatic atopic patients during seasonal exposure (26,41,42).

SIT is a useful treatment for allergic rhinitis, especially when the range of allergens responsible is narrow. As with all forms of SIT, it is important to select patients appropriately. The allergic basis of the rhinitis should be carefully assessed based on both history and skin or blood test results, and other causes of nasal symptoms should be excluded. Direct challenge

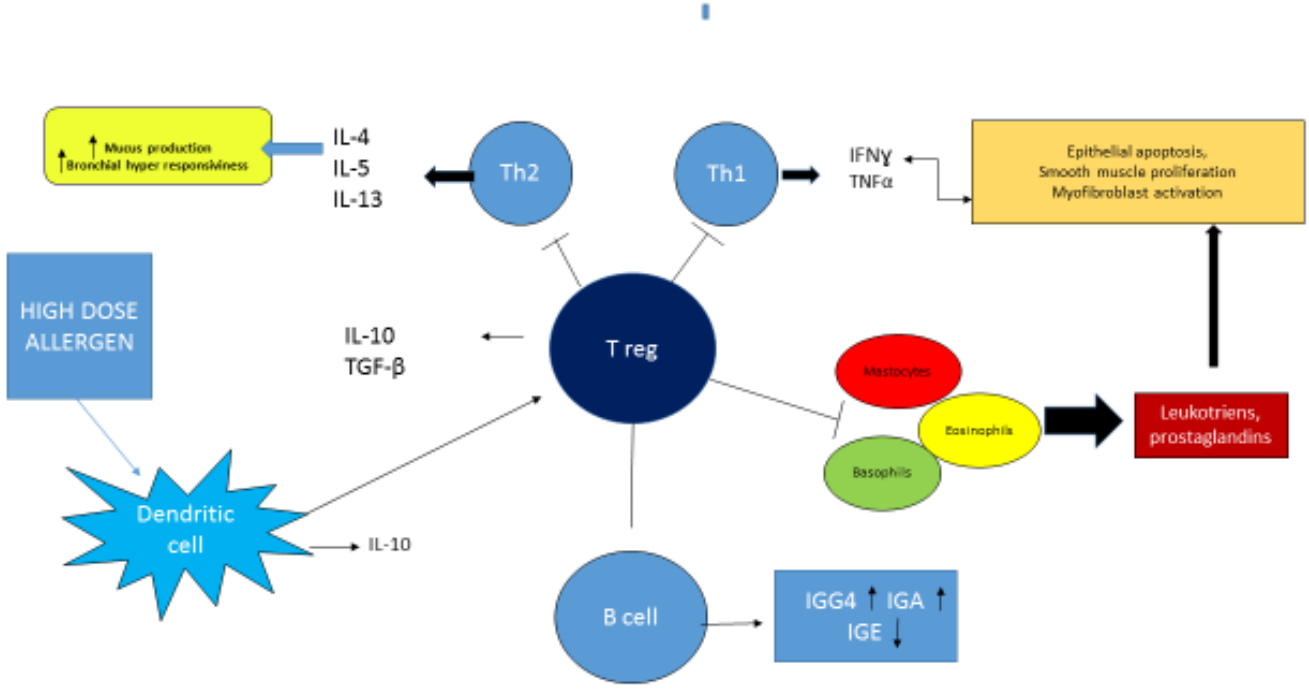

Figure 1. Mechanisms of subcutaneous allergen-specific immunotherapy. Systemic administration of high-dose allergen presumably leads to the activation of IL-10-secreting dendritic cells, which, in turn, contributes to the induction of Tregs. Mainly via the secretion of anti-inflammatory cytokines IL-10 and TGF-β, Tregs tend to re-equilibrate the immune response by limiting both Th1 and Th2 cytokine secretion and their detrimental effects on bronchial hyper-responsiveness, mucus secretion and bronchial remodeling, that is, epithelial cell apoptosis, smooth muscle cell proliferation, (myo)fibroblast activation and bronchial hyper-responsiveness. As a proposed mechanism, the secretion of IL-10 by Tregs induces B cells to secrete allergen-specific IgG4 and IgA, while limiting seasonal IgE upregulation.

tests to assess nasal sensitivity to allergen are not used in routine clinical practice but might be useful for assessing effectiveness in clinical trials.

SIT in children is indicated for nearly identical reasons as in adults (6) : 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 related allergen and the availability of an approved, standardized allergen extract (Table 1).

Efficacy of subcutaneous immunotherapy (SCIT) in allergic rhinitis

The effectiveness of SIT in patients with intermittent (seasonal) allergic rhinitis has been confirmed in many trials with grass, ragweed, and birch pollen extracts (43). Importantly, SIT has been shown to be effective even in patients with severe seasonal rhinitis caused by grass pollen that is resistant to conventional drug therapy (44). Importantly, some studies showed that patients with multiple allergic sensitizations responded at least as well as those who were monosensitized to grass pollen. The benefits of SIT for perennial rhinitis are less than those for seasonal rhinitis. In part, this reflects the difficulty in determining the extent to which allergy is responsible for perennial symptoms (15). Sensitization to house dust mite is common and does not always cause symptoms. Conversely, there are other causes of perennial rhinitis, including vasomotor instability, infection, and aspirin sensitivity. Nevertheless,

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 diseaserelated allergen (eventually by standardized provocation testing)
Allergen extract
Availability of a standardized allergen extract or preparation registered or approved by the authorities

clinical trials have shown a definite benefit in appropriately selected subjects. Clearer evidence has been obtained in patients with rhinitis caused by pet allergy. Several studies have shown a marked improvement in tolerance of cat exposure after SIT, which was confirmed both on challenge tests and simulated natural exposure (15).

For the Cochrane meta-analysis on the efficacy of SCIT in AR, 15 studies were selected for the evaluation (15). 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 immunotherapy by injection, especially in AR caused by polen allergens, is effective.

Efficacy of sublingual immunotherapy

Subcutaneous immunotherapy (SCIT) has been the traditional technique of administration for decades but it is flawed by the problem of adverse systemic reactions. An anaphylactic reaction, may be severe and though very rarely, even fatal. In recent years, sublingual immunotherapy (SLIT) has emerged as an actual treatment option because of its clinical efficacy and safety (45). The first studies on SLIT used low allergen dosages but it soon became apparent that much higher doses than those administered by SCIT were needed to expect clinical efficacy (46). The clinical efficacy of SLIT in AR, as for SIT in general, can be evaluated by a decrease in symptom scores of rhinitis and in the use of symptomatic drugs.

In 2005, when 22 randomized controlled trials (RCTs) were available, Wilson et al published the first meta-analysis on SLIT, which demonstrated a significantly higher efficacy of SLIT versus placebo, with an SMD corresponding to -0.42 for symptom scores (P = 0.002) and to -0.43 for medication scores (P = 0.00003). A further meta-analysis on SLIT in children, concerning only efficacy on AR, showed positive results (47,48). Ten RCTs with an overall number of 484 patients (245 actively treated and 239 placebo treated) were included, and a significant reduction of both symptoms (SMD -0.56, P = 0.02) and medication scores (SMD -0.76, P = 0.03) was found.

Of note, the subanalysis addressing the length of treatment and the kind of allergen administered demonstrated a higher efficacy for durations longer than 18 months and for pollen allergens compared with house dust mites.

Recent studies showed that the mechanism of action of SLIT is similar to that demonstrated for SCIT, and that when high doses are administered, immunoglobulin G-blocking antibodies, which were not found in SLIT studies employing low doses, are produced in significant amounts and persist after the discontinuation of treatment (48,49).

SCIT induces changes that skew Th2- to Th1-type response (immune deviation) related to an increased IFN-g and IL-2 production, with a reduction in Th2 activity, through a mechanism of anergy or tolerance, the latterbeing related to the generation of allergen-specific T regulatory (Treg) cells, which produce cytokines such as IL- 10 and TGF-b (50). The sublingual route of administration was suggested to have similar mechanisms as SCIT, with a particular involvement in mucosal dendritic cells (38,39).

Side-effects and compliance

The most obvious risk of SCIT is that of provoking a systemic allergic reaction. 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 (51). 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 (52). In the United Kingdom between 1957 and 1986, 26 fatal reactions caused by SIT were reported to the Committee on Safety of Medicines (53). SIT induces local reactions which are expected. In case of local regional reactions, the doses must be reduced and the re-ascension of doses is more progressive. Syndromic reactions are frequent (rhinitis, conjunctivitis, asthma) and must also induce a dose reduction (54). Asthma attacks can be severe and mainly occur in asthmatics. It was clearly shown that the SIT-induced asthma attacks occurred more frequently during the dose-increase period and the risk associated with immunotherapy to be drastically reduced when treatment is carefully monitored (55).Sublingual immunotherapy is much safer. Post-marketing studies reported rare and mild adverse events in adults and children (56,57). In the update review by Passalacqua, only 17 serious adverse reactions during SLIT were reported among all the controlled studies published between 2000 and 2006 (58). No fatal event has been reported in any study. They rarely induced an interruption of the treatment. The majority of these reactions were local, very mild (oral itching or swelling), and self-resolving. Interestingly, adverse effects were similar in children aged of 5 years or less. With sublingual grass allergen tablets, no severe side effect was reported in any study, and most adverse effects were observed at high non-recommended dosages (>500 IR) (59). However, it must be stressed that the risk of severe anaphylaxis, although exceptional, still exists with sublingual immunotherapy (60). Sublingual immunotherapy (SLIT) requires a commitment by the patient to a long-term daily maintenance therapy that is self-administered, and compliance is likely to be lower than that obtained in supervised clinical trials. A United States study reported an attrition rate of approximately 40 percent over four years (61). Several European studies have assessed the compliance and adherence with SLIT: A study of 300 children (6 to 16 years of age), who received either grass or house dust mite sublingual drops or tablets over two years of treatment, revealed that discontinuation rates were clearly tied to follow-up visits to the study site (62). The drop-out rate was 30, 68, and 82 percent in patients evaluated in the clinic every three, six, and 12 months, respectively. Another study, which focused on young children (three to six years of age) reported that 46 percent of 150 children discontinued SLIT within three months of initiation (63). The most frequent reasons for discontinuation were lack of effect, time commitment, and adverse events. A third study addressed a more realistic measure of surveillance: drug sales figures (as opposed to marketing surveys, which can overestimate compliance due to contact of patients by the surveyor). In postmarketing surveys, compliance ranges from 50 to 90 percent depending on age and duration of treatment. In contrast, data on SLIT prescription refills shows a different picture: sales decreased from 100 percent to 44, 28, and 13 percent, in the first, second, and third years, respectively (64). Of the total prescriptions for SLIT from the two major manufacturers that participated in the survey,

less than 20 percent of prescriptions were continued after three years. In a retrospective analysis of 6486 patients beginning subcutaneous immunotherapy (SCIT) or SLIT, 23 percent of SCIT patients, and 7 percent of SLIT patients completed three years of treatment (65). Although these rates of treatment adherence are not dramatically different from those for other chronic diseases, they may significantly impact efficacy. Noncompliance should not impact safety, provided patients are clearly instructed not to take extra doses in an attempt to "catch up" if they have had gaps in treatment. This may be particularly important at times when symptoms are severe. Long-term surveillance reporting will be needed to ascertain with the impact of stopping-restarting therapy. Although these rates of treatment adherence are not dramatically different from those for other chronic diseases, they may significantly impact efficacy.

Conclusion

EAACI recommended that subcutaneous SIT is indicated in children above 5 years of age and adults during pollen-induced allergic diseases (grass, birch, ragweed, olive, parietaria, cypress), house dust mites and cat allergies when avoidance is not effective. As pollen avoidance is elusive and as the proof of efficacy of mite avoidance is limited, SIT can probably largely be considered. Multiple allergen therapy is not recommended. SIT is indicated in patients above 5 years of age with allergic rhinoconjunctivitis and asthma, sensitive to birch, grasses, cypress, olive, parietaria or house dust mites. SIT may be considered in patients insufficiently controlled by antiallergic drugs, such as antihistamines and/or inhaled (nasal or bronchial) steroids. The insufficient control of rhinitis and/or asthma relates to the persistence of symptoms and use of reliever medications despite the use of these controllers. However, as asthma has to be controlled to avoid adverse events of SIT as far as the injective route is considered SIT is designed in that case to decrease the weight of controller treatments rather than as an add-on therapy.

As with any therapy, the risks and cost-effectiveness of SIT need to be assessed on a case-by-case basis. Current drug therapy for rhinitis can be very effective, but a significant minority of patients have suboptimal control of their symptoms. Some patients with rhinitis experience nosebleeds from intranasal steroids or excessive drowsiness from their antihistamines; others find pharmacotherapy inconvenient or ineffective. Moreover, we are now more aware of the adverse effects of rhinitis on quality of life. SIT offers a useful option for these patients, as well as a logical approach to dealing with the underlying problem.

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