REVIEW

History of Allergology: Allergen-specific Immunotherapy (AIT) the Identity Therapy of Allergology

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Abstract

Aim: **The aim of this review is to walk through the evolution of the art and science of allergic immunotherapy (AIT).**

Data sources: **Original reports related to the evolution of the concept of respiratory allergy and its specific treatment were identified by following references in journal articles, review articles, and allergy textbooks from the mid-19th century to the present.**

Study selections: **Studies highlighting milestones in the evolution of allergy immunotherapy practice were included.**

Results: **The history of AIT begins with the recognition of hay fever (hay fever) as a distinct entity and subsequent studies that established grass pollen as one of the causes. This knowledge led Noon, an English researcher, to induce tolerance toward pollen by administering phleum pratense pollen extract with subcutaneous injections (SCIT) to patients with hay fever.**

After the publication of Noon and Freeman's work in 1911, the practice of AIT spread rapidly and was used for many other allergens for the treatment of seasonal and perennial rhinitis, and asthma. The success of AIT was due, in large part, to the lack of drugs. Early studies were anecdotal, but over the past 60–70 years, studies on AIT have been conducted with increasingly sophisticated scientific methods. Nowadays, AIT is based on solid immunological basis and controlled trials (RCTs), while the clinical response of patients to AIT has not yet been established with certainty.

Conclusion: **Both the art and science of AIT have been supported by clinical and immunologic studies, yet its current role in clinical practice is debated because AIT is still a niche treatment, used only by some allergists.**

Keywords: AIT, SCIT, SLIT, RCT, IgE, Pollen, House dust mites

1. Introduction

It has been proposed to use the term allergy immunotherapy (AIT) to refer to therapies that aim to induce immune tolerance toward respiratory allergens [1].

The study of allergic respiratory diseases began about 200 years ago, and subcutaneous administration of AIT was introduced more than 100 years ago. The art and science of AIT have evolved over more than a century of use, and today can rely on numerous studies both immunological and clinical. For the majority of allergists, AIT, the identifier of this branch of medicine, is, not only the most effective treatment for allergic rhinitis, but also the only treatment that can change the natural history of the disease [2]. In this article we will review the evolution of the practice and knowledge behind AIT.

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1.1. Discovery of hay fever and its causes

In 1819, Bostock J., an English physician, presented the first detailed description of a symptomatology, unusual and troublesome, occurring annually from the middle of June, with ocular, nasal and pulmonary symptoms, which he called 'catarrhus aestivus.' [3] Nine years later, he published 28 cases of catarrhus aestivus [4], in which he hypothesized that the symptoms were caused by heat and sunlight, but reported that it was the common belief that the symptoms were induced by the smell of new hay, and so he called this clinical picture 'hay fever.' Bostock believed that this clinical condition mainly affected members of the English upper class. Studies on the cause of hay fever were performed and published by Blackely C.H, an English homeopathic physician, himself suffering from catarrhus aestivus or spring hay fever [5]. Blackely analysed all etiological hypotheses, rejected them all except that of phleum pratense pollen. To establish that phleum pratense was indeed the cause, he instilled phleum pratense pollen into his nose, out of season, reproducing typical symptoms of hay fever. The same researcher then created the first pollen diary by counting the number of pollens in the air daily and demonstrating a correlation between pollen counts and hay fever symptoms. Blackley reported in his book that from year to year the prevalence of hay fever increased, and that it was rarely observed in farmers. In the same years as Blackley, Wyman M., an American physician, described his experiments showing the presence of out-of-season respiratory symptoms from inhalation of ragweed pollen, establishing that this pollen was the cause of 'Autumnal Catarrh.' [6] Wyman described 83 cases and noted a familiarity among his patients, noting that respiratory allergy symptoms differed from individual to individual and could include catarrh aestivus, chronic asthma, and Autumnal Catarrh. Wyman had also noticed fewer sick people in the less affluent social classes, perhaps because of the hygienic conditions of housing.

2. Early attempts at specific treatment of hay fever

In those years there were no drugs to control nasal symptoms. Despite Blackley's empirical demonstration that spring hay fever was caused by phleum pratense pollen, alternative etiologic theories attributing the symptoms to infection, plant odour emanations, or hysteria came to predominate in Europe over the next 3 decades [7]. Dunbar W., an American researcher working as director of the State Institute of Hygiene in Hamburg, Germany, confirmed in 1903 that phleum pratense pollen was the cause of hay fever, using a methodology similar to that used by Blackley. Dunbar proposed that the cause of nasal symptoms was a toxin that was present in the pollen, and that only some people were susceptible to this toxin. A young associate of Dunbar's, Prausnitz C., like Dunbar, had hay fever symptoms in June. Both decided to treat themselves with injections of undiluted phleum pratense pollen extract, and both had severe systemic reactions. Perhaps influenced negatively by this experience and positively by the generation of diphtheria antitoxin in horses, Dunbar decided to produce an antiserum by injecting horses with phleum pratense pollen. The horse serum was then used in powder form, and applied locally to the eyes and nose daily as prophylaxis for hay fever symptoms, with mixed results. Because some patients became sensitized to horse serum, Dunbar decided to try active immunization in one patient. For previous severe reactions with injection of phleum pratense extract, he decided to inject a mixture containing phleum pratense extract and horse antiserum in a pattern of 15 escalating doses. He published a 100-fold increase in the threshold of the conjunctival reaction to phleum pratense and that, during the following grass pollen season, the patient reported a major reduction in symptoms compared with previous years [7]. After this insight, in 1911, Dunbar began treating patients with phleum pratense extract alone.

Also in 1911, Noon L. and Freeman J., who had both attended Dunbar's laboratory in Hamburg, accepted the theory that hay fever was due to an idiosyncratic sensitivity to a toxin present in the grass pollen, and, therefore, hypothesized that treatment by subcutaneous injection induced an antitoxin [8]. In the same 1911 article, Noon [8] outlined the methodology of injection therapy for hay fever. He treated some patients during the winter and spring, before symptoms developed; began treatment with small doses of phleum pratense pollen extract, and increased the intervals between injections by monitoring the clinical response and measuring the increasing threshold of conjunctival challenge with phleum pratense pollen extract. After Noon's untimely death from tuberculosis, his studies, were continued by Freeman, who published the follow-up results of 84 patients treated for 2–3 years with the therapy devised by Noon [9]. He published that the symptoms of hay fever were completely controlled with subcutaneous administration of phleum pratense pollen in 30 percent of cases, much improved in 35 percent, little

improved in 24 percent, and unimproved in 12 percent.

Just as pollen was originally shown independently to be the cause of hay fever, it was also shown that subcutaneous administration, used independently in both England and the United States, was clinically effective in controlling nasal symptoms from phleum pratense and ragweed, respectively. Koessler K., published in 1914, the results of 41 patients treated with ragweed extract administered subcutaneously. A total of 36 patients, were suffering from autumn hay fever, and were treated with ragweed pollen extract, starting in May and reaching the maintenance dose in August. The conjunctival test was helpful in determining the initial dose to be administered, but not in determining subsequent doses. Patients had to return each season for several years for the treatment to continue acting on nasal symptoms. Overall, only 8 of the 41 patients showed no improvement. Koessler rejected the toxin theory of Dunbar, Noon and Freeman, and hypothesized that the pollen protein acted as a sensitizer, providing a satisfactory explanation for individual susceptibility to the disease [10].

2.1. Adoption of subcutaneous immunotherapy as a treatment for other allergens causing rhinitis and asthma

In 1915, Cooke R. published his experience with active immunization. Like Koessler, Cooke believed that hay fever recognized the mechanism of protein sensitization. Cooke used intradermal skin tests to demonstrate sensitivity, noting that virtually all cases of hay fever had multiple sensitizations. He alerted physicians of the time to avoid this therapy in highly sensitized individuals, particularly those with associated asthma, because of the possible intense, even fatal, reactions that could occur after the use of a high dose of the allergen extract [11].

Also in 1915, Goodale J.L [12]. published a new scheme for therapy, using in 123 cases of hay fever continuous treatment for 12 months. Unlike Cooke, who used the intradermal skin test, Goodale determined the initial doses with the scratch test and noted that the skin reaction decreased with pollen treatment [12].

Clowes, in 1913, had published that in individuals sensitized to both grasses and ragweed, immunization against grasses did not confer protection for ragweed, hypothesizing the specificity of immunization [13].

The use of injection therapy quickly expanded from pollen to other inhalant allergens and from hay fever to asthma. In 1917, Walker C. published that he had successfully treated patients with asthma using extracts of cat, dog, and horse epithelium for treatment [14].

3. The discovery of the house dust allergen

Richard Kern, in 1921, had published that dust from known sources such as mattress dust caused asthma [15], but it was Cooke R. [16], in the following year, who reported the presence of a unique sensitizer in house dust to which many of his patients reacted. In 1924, Dutch physician van Leeuwen W.S., published that in 100 asthmatic patients he found very few cases that could be attributed to true specific hypersensitivity. He did note, however, that two extracts gave positive results in skin tests and exacerbated these patients' asthma when exposed: dusty wheat and wheat contaminated with *Penicillium glaucum* and *Aspergillus fumigatus*. He then noticed that in some parts of the Netherlands asthma was less severe than in other parts of the nation. He attributed these differences to the different degree of humidity. He finally observed that Dutch asthmatics reported that, in the mountains above 1500−1800 m, asthma symptoms improved but recurred, even with more severe symptoms, when they returned to their homes [17].

In 1929, Dekker H. a German physician, published an article, reported by Unger, in which he presented the case of a patient in whom asthma arose only in his bedroom, and to whom he found a strongly positive reaction to the extract of dust from his room. Examining it, he found an incredible number of dead parasites. [18], Dekker did not, however, identify mites. The identification of the house dust mite was made by a group of Dutch researchers in 1967. These researchers showed that the house dust allergen was the same all over the world. Working with dust from homes without pets and using titrated skin tests to quantify potency, they showed that the house dust allergen was not fungal, bacterial or human in origin. They showed that it was a mite found in house dust, *Dermatophagoides pteronyssinus*, particularly found in older and wetter homes in the city, and that the mite's body and faeces contained an allergen whose potency correlated almost perfectly with that of house dust extract [19].

4. Preparation of allergenic extracts

Noon prepared extracts for conjunctival testing and treatment by extracting phleum pratense pollen in distilled water and boiling it for 10 min. Clock

R.O. modified the extracts, adding glycerine so as to prolong the potency and tolerance of the extracts [20]. Methods to make the extracts more standardized and reliable were developed by Coca A.F., who used degreasing, extraction in normal salt solution with addition of sodium bisulfide, and sterilization by filtration [21]. In 1934, Sledge R.F., published a study in which patients had received alum-treated extract therapy, reporting that *constitutional* reactions decreased in frequency and severity and the total number of injections could sometimes be reduced [22]. In 1947, Loveless M.H., used pollen extract therapy emulsified in mineral oil, demonstrating that he could administer a 10-fold higher dose of allergen with emulsion allergen instead of aqueous extract [23]. Allergists, who usually administered single injections at lower doses, reported less favourable clinical results [24]. Due to the occurrence of local nodules and abscesses, the use of oil-emulsified allergen therapy was also abandoned because of safety concerns [25].

Another approach to improve the safety of the extracts was to treat the extracts in aldehydes, producing *allergoids*. With this technique, similar to that used to obtain anatoxin from bacterial toxins, Marsh, by inducing protein aggregation, decreased the allergenicity of the extracts while preserving their immunogenicity [26]. Extracts with alum and allergoids, were used for subcutaneous immunotherapy (SCIT) in Europe. An important improvement in allergenic extracts was the standardization by the Food and Drug Administration of extracts from cat epithelium, D pteronyssinus, D farinae, short ragweed, Bermuda grass, and several wild herbs in the 1980s and 1990s [27].

Today, researchers in the AIT industry are engaged in the application of recombinant technology to the production of allergenic products to achieve greater safety and convenience than that achieved with natural extracts.

Two approaches that had attracted great interest but were later abandoned were: stimulation of Toll-like receptor-9 with cytosine phosphodiesterase guanine (CpG) mimicking bacterial DNA [28] and production of peptides directed toward T-cell epitopes [29].

5. Variable treatment schemes

Noon [8], and those who immediately followed him [9−11], administered pollen extracts in a preseasonal and seasonal mode. With the use of AIT with house dust and animal dander, a *perennial* scheme was adopted, as suggested by Goodale in 1915 [12] The advantages of also administering pollen extracts with a perennial scheme soon became apparent. Treatment could be started at any time of the year, there was less urgency in reaching maintenance doses, and the allergist could reach higher doses [30]. An alternative treatment scheme, was introduced in 1930 by Freeman who referred to it as *rush immunotherapy* [31].

Rush SCIT with aeroallergens has been used until 2013 [32], but it is difficult to assess the real importance of this mode of administration because of the heterogeneity of studies and the lack of a single scheme that defines rush SCIT compared with other immunotherapy protocols [33]. The main advantage of rush SCIT, is reaching the maintenance dose faster, reducing the number of patient visits to the allergist's office. The safety of classical SCIT, which has scaled back its use in clinical practice [34], is certainly the most important factor that has limited the use of rush SCIT with aero allergens. The highest risk of systemic reactions is in the range of 15 %−100 % of patients [33]. The use of depigmented-polymerized extracts improved safety, with systemic reactions occurring in less than 2 % of patients [35].

6. From reagin to immunoglobulin E

The understanding of the mechanism of allergy coincided with the discovery of a substance present in the serum of patients with allergy. This substance was referred to as *reagin*, which, present in the serum of the allergic patient, could be transferred to the skin of a nonallergic subject, who received the allergen, to which only the donor of the serum was sensitized. In the study that showed the presence of the reagins, the serum of Küstner H, who was allergic to cooked fish, was injected into the subcutaneous skin of Prausnitz C. The passive transfer site showed an inflammatory reaction after 1−2 h that Prausnitz ate fish, and after injection of cooked fish extract, 24 h after transfer [36]. The passive transfer, called the P−K test, using the authors' initials, allowed allergists to quantify the amount of skin sensitizing antibody (SSAb), or reagin, was present not only initially but also during the course of AIT.

Cooke and his collaborators published a 2- to 4-fold increase in SSAb after the first few months of AIT, which was followed by a decrease at the end of the first year of treatment. They followed patients for the next 7−10 years of treatment [37].

In 1967, reagins were isolated, almost simultaneously, by Ishizaka K. and Ishizaka T [38]. in the United States and by Johansson S.G. and Bennich H [39]. in Sweden, and were subsequently identified as immunoglobulin E (IgE).

7. From the blocking antibody to IgG4

Cook had described the presence of a circulating substance, later to be called a *blocking antibody*, which was not present before AIT but was found after one year of AIT [40]. After some initial enthusiasm, because the finding of the blocking antibody was thought to explain what might have been the mechanism of the clinical improvement achieved with AIT, in later studies there was no evidence of a correlation between the titters of the blocking antibody and clinical outcomes [41]. Subsequently, the blocking antibody was identified in the IgG4 subclass, which represents the humoral response to prolonged antigenic stimulation as in the case of AIT [42]. However, the correlation between specific IgG4 and clinical response to AIT was also not significant. However, 2 functional IgG4 assays, one that assessed competition for allergen between IgE and serum inhibitory antibodies and the second that assessed inhibition of CD23-dependent allergen presentation facilitated by IgE, revealed a significant correlation with combined symptom scores in a large immunotherapy study [43]. It should be pointed out that although the correlations were highly significant, the correlation (r) values were very low: −0.25 and −0.28, respectively [43].

8. Evidence for the effectiveness of AIT

8.1. Introduction to the randomized, double-blind, placebo-controlled study

The first randomized, double-blind, placebo-controlled study of AIT was conducted in England and published in the prestigious Lancet in 1954 [44].

Many allergists including Lowell F., were opposed to the use of randomized, double-blind trials to evaluate AIT. However, Lowell and Franklin, carried out a study in patients who were already receiving AIT in a mixture of allergens, which included ragweed, [45]. Lowell and Franklin published, evaluating only 24 patients, that: (1) AIT was effective for the allergen causing the symptoms; (2) that AIT was equally effective even when administered in a mixture of allergens as long as it contained the causative allergen; (3) that AIT was specific for the allergen causing the symptoms; and (4) that the efficacy of AIT depended on the administration of a high dose of the allergen extract [46].

A study deemed very important by AIT advocates was that of Johnstone D. begun in 1953 and published after a long follow-up of 14 years [47]. The results of this study argued that extracts with multiple allergens were as clinically effective as allergenic extracts administered separately. Both studies by Lowell and Franklin [45,46] and Johnston [47] had demonstrated the importance of adequate dosing in order to achieve the potential benefits promised by AIT. With the introduction of standardized extracts, many researchers conducted randomized, double-blind studies examining one or more doses of mono-allergenic extracts. From these studies, it was possible to determine appropriate and inappropriate doses for many pollens: grasses, short ragweed, birch; and for the most important indoor allergens: house dust mites, cat and dog dander [48]. In these publications, the optimal and suboptimal doses are expressed as the main allergen content of the maintenance injection. This is necessary because many of the extracts were standardized only by the manufacturer and dosing was expressed in units used by the manufacturer. Dosing information, however, was converted to units of potency by the U.S. Food and Drug Administration in the third update of immunotherapy practice parameters [49].

Despite support from leading allergy researchers, AIT has been challenged [50]. and has found less and less space in the leading Journals of Internal Medicine, despite major investments by the Industries that market AIT [51].

The evidence, that high doses of the allergenic extract are required for effective AIT, has been challenged by the practice of homeopathic dosing, or the *Rinkel method,* named after its originator, who published it in the second half of the 20th century, describing the results of his method *as very satisfactory* [52]. It was later shown by 2 double-blind, placebo-controlled studies published in the 1980s that the *R. method* was not effective [53−55].

9. Oral and sublingual immunotherapy (OIT and SLIT)

The first publications on oral administration of pollen extracts were published in 1900 [56]. Publications regarding oral administration presented both positive and negative results on the efficacy of this route of administration, but they came from studies with serious methodological deficiencies. Oral administration was judged in the USA after a study by 3 medical schools in Chicago and the University of Michigan as ineffective, despite the fact that the total oral dose was 200 times higher than the dose used by injection [57]. A final study was performed with cat dander extract administered orally but this study also showed the ineffectiveness of OIT [58]. In Europe, studies on OIT continued until 1997 [59−67].

The OIT approach has been superseded by sublingual administration (SLIT). Most advocates of

SLIT point to [68], the article by Scadding G. and Brostoff J [69]. as the first RCT performed with SLIT, omitting, however, that sublingual administration of allergens, had already been used and published by Hansel F [70]. and used in the private practice of many U.S. allergists, and that it had been described as ineffective in JAMA [71,72] and, in 1975, in J Allergy Clinical Immunology [56] in an article wanted by the *Executive Committee of the American Academy of Allergy* [73].

It is important to examine this publication in detail. Scadding and Brostoff published a double-blind placebo-controlled cross-over study administering low-dose sublingual droplet therapy (SLIT-D) with house dust mite. The therapy was effective in 72 % of the patient group treated with sublingual therapy ($P < 0.03$), improving nasal symptoms. Following SLIT with house dust mite, the authors showed a significant increase in peak morning nasal inspiratory flow ($P < 0.01$) in 13/18 patients who were clinically improved. They also showed that resistance to nasal challenge with house dust mite increased up to 1000-fold in some cases ($P < 0.05$). The authors concluded that oral therapy is safe and has no side effects that are very common with subcutaneous therapy. The authors pointed out that the efficacy of this form of therapy occurs quickly (2−4 days after initiation) but wears off after a week after discontinuing the drops.

This study initiated an important debate about the results obtained, which it is important to comment on because SLIT-D, after initially being shelved, was re-proposed by Stallergenes [74] and Abellò [75], and was indicated as an alternative to SCIT, which had been the route of administration of the allergenic extract since 1911 [8].

We quote and comment on Warner J.O.'s Editorial to the article by Scadding and Brostoff [76]: "Clinical allergy offers the opportunity to publish articles on all aspects of clinical and experimental allergy. If the studies are scientifically sound and of contemporary interest, they are likely to be accepted even if the topic is controversial."

Therefore, because of these considerations, Scadding and Brostoff's article was published because it was supposed to originate comments from Journal readers, who would make their own critical assessment. In fact, Scadding's RCT had only one very negative comment [77].

The literature had rejected the use of SLIT as unproven by any known immunological mechanism that could explain the phenomenon [78]. Therefore, since the underlying justification for Scadding's trial [69] was found to be unsound, and, although subcutaneous hypo-sensitization, pioneered by Noon [8] on the basis of an equally unsound theory, had an important success, important controversies about the role of AIT itself remain, even today [78].

The very short duration of the therapeutic response is difficult to support with an immunologic theory, and an effect on allergen-induced late reactions seems highly unlikely [78].

Reports on the efficacy of low-dose SLIT abound in the literature [79−81]. Scadding and Brostoff's RCT is the first double-blind evaluation and as such, according to evidence-based medicine (EBM) should be given due consideration [82].

Actually what Warner had hoped for did not come to fruition because Scadding's publication was directly commented on in only two publications [77,83] We will dwell, on the Position Paper by Malling et al. [83] which is the result of the working group on local immunotherapy of the European Academy of Allergology and Clinical Immunology (EAACI) Immunotherapy Subcommittee and the European Society of Paediatric Allergy and Clinical Immunology (ESPACI) Immunotherapy Committee. On page 938, about the work of Scadding and Brostoff [69] they wrote, "The publication was excluded from the position paper because the authors used low doses …. The treatment schedule and dosing used in this study bears little resemblance to the current administration and dosing of sublingual immunotherapy (SLIT). Scadding and Brostoff attributed the improvement not to hypo-sensitization but rather to desensitization of basophils." [69].

In the following decade, studies were conducted more in line with the current concept of SLIT, allowing SLIT to be mentioned for the first time in 1998 as a possible alternative to SCIT in a World Health Organization position paper [84], when only 5 randomized, double-blind, placebo-controlled studies could be cited. Currently, there are more than 100 randomized, double-blind, placebo-controlled studies published, and SLIT has become the route of administration for AIT in several European countries [85].

In the first decade of the 21st century, two SLIT-producing Industries developed fast-dissolving SLIT tablets (SLIT-T) in Europe. The first 2 were a 5-grass tablet and a phleum pratense tablet [86,87]. Both SLIT-Ts were studied with similar RCTs in which patients with allergic rhinitis were treated for 3 years and then observed for 2 seasons of grass pollen without further treatment. The main difference between the 2 studies was that the SLIT tablet of phleum pratense was administered continuously for 3 years [86], whereas the 5-grass tablet was started 2−4 months earlier and continued throughout the grass pollen season [87].

The results of the 2 studies were similar, and both demonstrated persistent benefit for the 2 follow-up seasons. In the United States, marketing of SLIT-T tablets with 5-grass, phleum pratense, and short ragweed was approved in 2014, and SLIT-T for mixed mites was approved in 2017. There are no preparations of SLIT-D, and it should be noted that the efficacy claims are not generic but can only be applied to the product under RCT [87]. Therefore, the evidence of efficacy of SLIT-T cannot be transferred to SLIT-D [87].

10. Conclusion and future perspectives

AIT was the first useful therapy in the management of respiratory allergic diseases, representing a milestone because it is specific to the allergen that causes it [1]. Many of the discoveries made in the field of allergology, have been used by the industries that market AIT. AIT, administered subcutaneously from 1911 to the present, was considered a niche therapy of allergic rhinitis because it was administered exclusively by allergists and because it was used for patients with a well-defined allergy diagnosis. It was clear that the economic profit of the AIT industries was decreasing because the cost of producing allergenic extracts was increasing, and the demands for new therapies were decreasing because of what was written by the British CSM, which in fact did not authorize SCIT in medical practices without cardio-respiratory rescue equipment being present and without supervision, for at least 2 h of the patient after SCIT. But perhaps the most dramatic message that could be read in this document was: « *Desensitising vaccines have the potential to induce severe bronchospasm and anaphylaxis, and these reactions have resulted in 26 deaths since 1957-5 in the past* 18 months. *The efficacy of the desensitising agents used in this country-apart from the bee and wasp venoms and the vaccines used to prevent anaphylactic reactions to some antibiotics -remains in doubt. At present there is no accurate information on the comparative efficacy and safety of these agents.*»

For these reasons, in the 1990s, the AIT industries, with the help of prominent AIT Opinion Leaders, and investing significant capital, dusted off an old AIT route of administration, the sublingual (SLIT), following a trial performed in 1986 [84]. The mantra repeated by the majority of trials performed with SLIT was that SLIT represents a significant advance, offering patients an excellent safety and convenience profile. From a historical perspective, the past three decades have witnessed an impressive development of SLIT, compared with the century-long history of AIT in general. To give pharmacological significance to SLIT, trials had to clarify many aspects: efficacy, safety, role of standardized allergen preparations, etc. In parallel, many issues emerged that were only partly clarified or not clarified: polyallergic patients, use of mixtures, preventive effects of SLIT, etc. To avoid do-it-yourself SLIT, two industries, ALK and Stallergen have registered SLIT in tablet form for grasses, mites, mugwort.

Looking at a historical perspective, the starting point and the end point, the question is *why is such an expensive and perhaps not so clinically effective therapy being used in the third millennium?* In this field, as in many fields of clinical research there is certainly a conflict of interest, involving both industry and opinion leaders.

In 2015, a meta-analysis [88] that analysed published RCTs with SLIT-T for grass pollen by ALK and Stallergen concluded: «*Findings show a small benefit of the grass pollen sublingual tablets in reducing symptoms and in decreasing the use of symptomatic medication (antihistamines and corticosteroids) in patients with SARC. Considering the low magnitude of the benefit, the convenience and easy administration do not seem to be sufficient reasons for the choice of SLIT.*»

Table 1 shows the comparison among AIT administered as subcutaneous, sublingual drop (SLIT-D) and sublingual tablet (SLIT-T). Each parameter reported was determined with guidelines based on [89].

On the other hand, molecular allergens have been used in clinical trials and allergology practice, but with the development of the allergen array, i.e., a bioinformatics platform that allows simultaneous analysis of a patient's sensitization to dozens or even hundreds of specific allergenic molecules, the strategy of using allergens in determining the IgE profile of allergic patients has changed [90]. This strategy is deeply integrated into the new approach of precision medicine, which aims to accurately characterize the patient's phenotype. In parallel, personalized medicine has been proposed, focusing on the patient's endotype, a biologically defined subtype of a disease, based on specific mechanisms that contribute to its development and progression [91]. The integration of precision medicine, based on the patient's IgE definition, with personalized medicine, based on the patient's clinical endotype, seems to be a winning strategy for the use of AIT in the allergic patient. Molecular allergy diagnosis (MAD) has been used in patients with sensitization to aeroallergens, food, latex, and hymenoptera [92]. In patients with aeroallergen sensitization, when AIT is selected, MAD will likely become the gold standard in the near future. This development

Table 1. Comparison among AIT administered as subcutaneous, sublingual drop (SLIT-D) and sublingual tablet (SLIT-T).

	SCIT	SLIT-D	SLIT-T
Benefit:	Improvement of symptom and medication use.	Improvement of symptom scores and medication use. There is some indication of less benefit from aqueous versus tablet SLIT, but the lack of standardized dosing across multiple trials does not allow for adequate comparison.	Improvement of symptoms, rescue medication, and QOL.
Harm	Risks of SCIT include frequent local reactions and rare systemic reactions, which may be severe and potentially fatal if not managed appropriately. This risk must be discussed with patients prior to initiation of therapy.	Common mild to moderate local adverse events. Very rare cases of systemic adverse events. No reported cases of life-threatening reactions	Local reaction at oral administration site and low risk of anaphylaxis.
Cost	SCIT is cost-effective, with some studies demonstrating value that dominates the alternative strategy with improved health outcomes at lower cost. Direct and indirect costs of AIT vary based on the third-party payer, the office/region, co-payment responsibilities, and travel/ opportunity related costs in being able to adhere to the frequency of office visits required.	Intermediate. More expensive than standard pharmacotherapy, but there are indications of lasting benefit and cost-saving in the long-term.	Intermediate. More expensive than standard pharmacotherapy, but persistent benefit may result in cost-saving in the long-term.
Benefits-harm assessment	For patients with symptoms lasting longer than a few weeks per year and for those who cannot obtain adequate relief with symptomatic treatment or who prefer an immunomodulation option, benefits of SCIT outweigh harm. The potential benefit of secondary disease-modifying effects, especially in children and adolescents, should be considered.	Appreciable benefit in patient symptoms and minimal harm.	Benefit outweighs harm.
Value judgments	A patient preference-sensitive approach to therapy is needed. Comparatively, the potential for harm and burden associated with medications are significantly lower, although the potential for benefit is also lower (with no potential for any disease-modifying effect or long-term benefit) as medications do not induce immunomodulation. Logistical issues surrounding time commitment involved with AIT may be prohibitive for some patients. The strength of evidence for SCIT efficacy, along with the benefit relative to cost, would support coverage by third party payers.	Aqueous SLIT improves patient symptoms and rescue medication usage with minimal risk of serious adverse events but common local mild adverse events. Single allergen therapy has been extensively tested. Multiallergen AIT requires future studies to validate its use.	Useful for patients with severe or refractory symptoms of AR.

(*continued on next page*)

Table 1. (continued)

	SCIT	SLIT-D	SLIT-T
Policy level	Strong recommendation for SCIT as a patient preference-sensitive option for the treatment of AR. Strong recommendation for SCIT over no therapy for the treatment of AR. Option for SCIT over sublingual immunotherapy (SLIT) for the treatment of AR.	Recommendation	Strong recommendation.
Intervention	SCIT is an appropriate treatment consideration for patients who have not obtained adequate relief with symptomatic therapy or who prefer this therapy as a primary management option, require prolonged weeks of treatment during the year, and/or wish to start treatment for the benefit of the potential secondary disease-modifying effects of SCIT.	High-dose aqueous SLIT is recommended for those patients who wish to reduce their symptoms and rescue medication use.	SLIT tablets are recommended for patients with severe or refractory AR. Epinephrine autoinjector is recommended in the FDA labeling for approved tablets due to the rare but serious Risk of anaphylaxis. Tablets for select antigens are available in various countries

challenges the historical beliefs of allergists from the last century, where a concordance between the patient's history, physical examination, and SPT results was considered sufficient to determine the appropriateness of AIT [93]. Using MAD, in patients sensitized to inhalant allergens, it will be possible to identify those that could better benefit from AIT, overcoming the current approach based only on the use of *extracts from allergen sources*, materials used for skin prick testing and specific IgE assay. The allergens, but also the components of individual molecules have different *in vitro* and/or *in vivo* allergenic activity, which must be evaluated. The ability to detect individual allergenic components offers to the clinician the opportunity to make a more precise diagnosis of allergic diseases using the approach referred to as *component-resolved diagnosis* (CRD) [94,95]. Indeed, distinguishing between genuine and cross-reactive allergen sources can help the clinician to define the most likely causal relationship between allergen exposure and allergic symptoms and to exclude irrelevant positivities provided by SPTs, in polysensitized patients. This approach is particularly important in patients who want to undertake AIT. This sort of *nonspecific* reactivity has been carefully considered in AIT protocols [96], and the risk of inaccurate IgE test results has been highlighted [97]. For example, in the presence of IgE positive for grasses such as *Phleum pratense*, Phl p 1 and Phl p 5 are genuine and major components, whereas Phl p 7 and Phl p 12, a polcalcin and a profilin, respectively, are cross-reactive components. Thus, a positivity for *Phleum pratense* should be evaluated at the molecular level. Indeed, it has been suggested that AIT is most effective in the presence of true sensitization, whereas sensitization with cross-reactive components has less chance of success [98,99]. Only after defining the endotype that patient, the rules will remain the same: pharmacological treatment and/or AIT will be proposed to the patient. Many authors have noted that, following an analysis of the IgE repertoire by MBD (Molecular-based diagnosis), the prescription of AIT was erroneous, showing that, in more than 50 % of patients, the results of MBD significantly changed the indication or selection of allergens for immunotherapy [100]. These results were confirmed by an Italian study [101]. These considerations should be supported by allergists, because the definition of the patient's IgE profile is necessary for the choice of therapies (from drugs to AIT). More complex diagnostics and in-depth knowledge of molecular allergy and its rules will certainly be helpful for the diagnosis and treatment of allergies, because they will improve the centrality of the allergist's role in allergic diseases

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Conflict of interest

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