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The evolution of allergen immunotherapy from empirical desensitization to immunological treatment

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Summary

In its century-long history, allergen immunotherapy (AIT), has shown continuous evolution in terms of the materials and the treatment schedules used, the adequate duration, and the mechanisms of action underlying its clinical efficacy. The passage from the empirical phase of AIT to the era of evidence-based medicine (EBM) was associated with achievement of the highest levels of evidence. This regarded both forms of AIT currently used, represented by subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In particular, SLIT tablet preparations of pharmaceutical quality provided physicians and patients a treatment whose efficacy had been confirmed with the highest level of scientific evidence and improved the credibility of AIT for the entire medical field. However, further advances are needed for AIT in terms of optimal patient selection and the required dosage, as well as the quality and composition of the allergen extracts, factors favouring compliance, and the most appropriate duration capable of maintaining the clinical benefit over time.

Introduction

Allergen immunotherapy (AIT) was introduced more than 100 years ago by Noon and Freeman, who investigated the effects of active immunization by injecting a grass pollen extract containing what they believed to be the symptom-causing "toxin" into patients suffering from seasonal allergy to grass pollen (1,2). The field of application of this treatment was hay fever, which was defined, after the first description by Bostock, as a relatively rare disorder that particularly affected the upper class, by the pioneering research by Charles Blackley, who was able to measure the pollen in the air and propose a pollen calendar (3). Some years later, a treatment for hay fever was introduced by Dunbar, based on passive immunization of patients by serum from horses (serum anti-toxin) that had been actively immunized by injections of pollen (4). At present, we know that such an approach is inappropriate and very dangerous, but the experiments by Dunbar in Hamburg drew the attention of other researchers, and particularly that of Noon and Freeman, who understood that active immunization of patients with pollen extracts was a more suitable treatment. Their studies showed the clinical benefit of desensitization, but also highlighted its limit, which is the possible occurrence of anaphylactic reactions. The "pollen vaccine" was an empirical treatment based on administration of increasing amounts of raw pollen extracts whose content was unknown (1,2). In 1933, Cooke introduced the first method for assessing the content of allergen extracts, using pollens from grasses and ragweed, by measuring the amounts of proteins (5). Desensitization was applied quite extensively as an empirical treatment, but it took many years to

demonstrate that this treatment was efficacious by performing a clinical trial, which was first performed by Frankland and Augustin in 1954 (6).

The discovery, since the late 1960s, of the key players in the immune response to allergens, such as IgE and IgG blocking antibodies, T cells, and the cytokine network, facilitated the understanding of the immunological changes induced by administering the causative allergen and the appropriate use of the term "immunotherapy" for this type of treatment (7). The recognition of the scientific basis of AIT paved the way for the era of double-blind placebo-controlled trials. The results from these trials allowed for significant advances, such as identification of the clinically effective doses (measured in micrograms) of the major allergens from the most common causative agents, including pollens, house dust mites, and animal epithelia (8). The body of findings from these trials, most of which were based on small populations of patients, generated information that shaped expert opinions in a consensus document on AIT (9-11). At the same time, the doses associated with systemic adverse effects were highlighted; this indicated dosages with a good balance between efficacy and safety for the different allergens (8). In fact, in the 1980s, the issue of safety emerged as an important limit for AIT, with a series of severe systemic reactions reported both in the UK and USA (12,13). Among a number of proposals for improving the safety, including injective material based on allergoids or other allergen modifications (14), the use of adjuvants enabling reduction of the allergen dose in the extract (15) and other routes of administration, such as the nasal (16), oral (17), and sublingual routes, were proposed. The latter route, which was initially proposed in 1986 (18), proved to be an effective alternative to the injection route. This was initially acknowledged in the World Health Organization (WHO) position paper on AIT in 1998 (19) and later evaluated in detail in a dedicated document (20).

Today, both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are generally recognized as the two recommended forms of AIT for respiratory allergy, with their use depending upon the physician's choice, according to the patient's characteristics and preferences. This choice can be appropriately guided by the body of knowledge provided by the evidence-based medicine (EBM) data. In fact, the high number of controlled trials available for SCIT and SLIT allowed meta-analyses to be performed, which when positive, are currently considered to be the method that attributes the highest grade of recommendation, i.e. the Ia, to any medical treatment (21).

Data from EBM

Since 1995, Abramson and co-workers performed a Cochrane systematic review of placebo-controlled trials of SCIT in asthma, based on the standardized mean difference (SMD) between active and placebo treatment, which was periodically updated (22-24). The latest update was made in 2010 and included 88 trials: 42 on house dust mite allergy, 27 on pollen allergy, 10 on animal dander allergy, 2 on *Cladosporium* mould allergy, 2 on latex, and 6 on multiple allergens (24). A significant improvement was found in asthma symptom scores (SMD, -0.59; 95% CI, -0.83 to -0.35), and the data indicated that it would have been necessary to treat 3 patients with SCIT to avoid one deterioration in asthma symptoms and to treat 4 patients to avoid one requiring increased medication. SCIT significantly reduced allergen-specific bronchial hyperresponsiveness (BHR) and also reduced non-specific BHR. The authors concluded that SCIT reduces asthma symptoms and asthma medication use and improves BHR; furthermore, they noted that, in a randomized controlled trial (RCT), the level of benefit obtained was comparable to those for inhaled steroids.

Thus far, there has been only one reported meta-analysis on the efficacy of SCIT in rhinitis, which was performed by Calderon et al. in 2007; this included 51 trials (25). Symptom score data from 15 trials were suitable for the analysis and showed an overall reduction in the SCIT group (SMD, -0.73; 95% CI, -0.97 to -0.50; $p < 0.00001$). Medication score data from 13 RCTs were suitable for analysis and showed an overall reduction in the SCIT group (SMD, -0.57; 95% CI, -0.82 to -0.33; $p < 0.00001$). The authors concluded that use of SCIT in appropriately selected patients with seasonal allergic rhinitis results in a significant reduction in symptom scores and medication use.

The first meta-analysis on the efficacy of SLIT was performed in 2005, when 22 RCTs were available (26), and demonstrated a significantly higher efficacy of SLIT versus placebo, with an SMD corresponding to -0.42 for symptom scores ($p = 0.002$) and corresponding to -0.43 for medication scores ($p = 0.00003$). The authors did not detect differences according to subgroups, such as patients' age and the type of allergen, because of the relatively low numbers. This was assessed in subsequent analyses. In 2006, a meta-analysis on the efficacy of SLIT in children with rhinitis was published and included 10 RCTs with an overall number of 484 patients (245 on active treatment and 239 on placebo). A significant reduc-

tion in both symptoms (SMD, -0.56; p = 0.02) and medication (SMD, -0.76; p = 0.03) was observed with SLIT (27). Interestingly, a sub-analysis addressing the length of treatment and the type of allergen administered demonstrated a higher efficacy for durations longer than 18 months and for pollen allergens compared to house dust mites.

In 2010, the global meta-analysis on rhinitis was updated and included 49 RCTs, comprising 2333 patients treated with SLIT and 2256 treated with placebo (28). Significant reductions were confirmed for symptoms (SMD, -0.49; 95% CI, -0.64 to -0-34; p < 0.00001) and medication scores (SMD, -0.32; 95% CI, -0.43 to -0.21; p < 0.00001) in favour of the active treatment.

Of note, in another meta-analysis on patients with asthma, the number needed to treat to avoid one patient with maintained or worsened symptoms was 3.7; this was comparable to that reported above for SCIT in asthmatic patients (29).

Further recent meta-analyses addressed the type of allergen. Concerning house dust mites, a meta-analysis on SLIT with mite extracts, showed, as stated by the authors, "promising evidence of efficacy" but suggesting "more data, derived from large, population-based, high quality studies" (30). Meta-analysis limited to studies on grass pollen allergy found that SLIT significantly reduces both symptoms (SMD, -0.32) and medication use (SMD, -0.33) compared with placebo. In addition, the authors noted that SLIT is more efficacious in adults than in children, and that prolonging the duration of pre-seasonal treatment for more than 12 weeks improves the treatment efficacy (31).

Data from the "big trials"

Even meta-analysis may be criticized, due to the limitations introduced by the heterogeneity of the included studies, which, when statistically analysed, is generally highly significant. Such limitations can be obviated by single studies conducted on large numbers of patients that allow for adequate statistical power. The recent studies on SLIT administered by tablets of grass pollen extract, performed to obtain the registration of the products by the European Medicine Agency, evaluated large populations, comprised of 855 adults treated by a timothy-grass extract (32), 628 adults treated using a 5-grass pollen extract (33), and 278 children treated using the same 5-grass preparation (34). These studies, known as "big trials", showed a highly significant improvement in symptoms and rescue-medication scores in actively treated compared with placebo-treated patients during the grass pollen season.

In addition, the big trials provided important observations concerning the dose-dependence of clinical efficacy: only high doses, corresponding to 75.000 Standard Quality (SQ) in the trial with the timothy-grass pollen (32), and to 300 Index of Reactivity (IR) in the trial with the 5-grass extract (33), were effective. A notable finding was reported by Devillier et al, who performed a post-hoc analysis of data from two big trials with the same product (33,34). The analysis made apparent that the magnitude of efficacy was higher in patients with more severe symptoms during the grass pollen season. In fact, for the trial in adults, the differences in the symptom-medication score in the active versus placebo group were 15%, 26%, and 37% for the low-, moderate-, and high-severity tertiles, respectively; in the paediatric trial, these values were 10%, 33%, and 34%, respectively (35). By calculating the monthly cumulative dose, the World Allergy Organization Position Paper on SLIT suggested 600 mcg of the grass pollen major allergen Phl p 5 as an optimal dose (20). This makes SLIT comparable, although provisionally limited to grass pollen extracts, to SCIT, in terms of dose-dependence. In fact, for the latter, the amounts (in micrograms) of the major allergens that should be administered in the maintenance phase for clinical efficacy have long been known in the case of the most common allergens (including ragweed pollen, dust mites, and cat epithelium) (8).

Of note, recent studies showed that SLIT acts by mechanisms similar to those of SCIT (36,37). Indeed, both treatment approaches are able to modify, through allergen capture and presentation by dendritic cells, the pattern of response of T-cells, which in allergic subjects is characterized by the prevalence of the Th2 type. The induced changes result in a Th1-type response (immune deviation), related to increased interferon (IFN)-gamma and interleukin (IL)-2 production or to reduced Th2 activity, through a mechanism of anergy or tolerance. It is now known that T-cell tolerance is characterized by the generation of allergen-specific regulatory T-cells (Treg cells), which produce cytokines, such as IL-10 and transforming growth factor (TGF)-beta, with immunosuppressant and/or immunoregulatory activity (38).

A very important outcome from the big trials evaluating the new sublingual preparations in tablet form was the fulfilment of the rigorous process of registration as phar-

maceutical therapies, which is required by regulatory agencies. Such methodology, currently applied only for grass pollen, is based on precise procedures of standardization and offers physicians and patients preparations that are comparable to drugs. It is crucial that, in the coming years, allergen extracts containing the clinically important allergens are obtained, expressing these amounts in micrograms, and excluding irrelevant molecules that are unlikely to be involved in clinical benefit.

Requirements for further improving the clinical outcomes of AIT

A recent review highlighted the issues in the further development of optimal patient selection, dosage, and treatment duration (39). Regarding the first point, as stated above, the physician's choice of the allergen extract and the route of administration to be used must be based on the patient's characteristics and preferences. A critical issue to be considered is compliance: it is known that SCIT has a lower compliance than SLIT because of the inconvenience of frequent visits (particularly in the build-up phase) to the allergist's office to receive the injections (40). Furthermore, SLIT also has compliance problems, particularly due to the cost, the ability to manage the local reactions, and the need to continue the treatment for the duration required to ensure lasting effects, but most of these issues can be overcome by adequate education of the patient (41). Other aspects influencing compliance are the patient preference concerning the schedule (pre-co-seasonal schedules are less demanding than continuous schedules) and the perception of efficacy in relation to the administered dose (this is also influenced by education of the patient).

An issue often overlooked in choosing the extract is the adequacy of the allergen composition in terms of the patient's IgE profile. For example, it was recently shown that grass extracts containing only *Phleum pratense*, which proved effective for patients living in Northern Europe (32), may be inadequate for patients living in the Mediterranean area. In fact, it was demonstrated by both immunological (42) and botanical (43) studies, that an extract containing five grasses fit such patients' profiles better than the extract containing only *Phleum pratense*. In particular, by using phenology methods, relevant differences were found between grass pollen count and effective flowering of the grass species. Only some species contributed to the grass pollen peak, and important species, including *Phleum pratense*, were not present during the peak in northern and central Italy; this had an obvious effect on the choice of appropriate AIT (43).

Concerning the dosage to be administered, for SCIT, the balance between efficacy and safety must be accurately analysed in individual patients, and in particular in asthmatic patients, because of the risk of systemic reactions, as indicated by a recent meta-analysis also (24). SLIT is much better tolerated, with the most common side effects being local reactions in the mouth or in the gastrointestinal tract (44), while the risk of anaphylaxis is extremely low. However, anaphylactic reactions may occur if incongruous mixtures or very high doses are used (45) or when patients admitted for SLIT because of previous systemic reactions to SCIT start the SLIT treatment with no up-dosing regimens (46). Another important aspect related to the dose for administration is that the potency of the allergen preparation should not be expressed in arbitrary units (which does not allow for the preparation of comparable formulations by different producers), but should be titrated in terms of micrograms of major allergens, which would ensure that the exact dose prescribed is clear to the allergists and patients, as stated by the World Allergy Organization Position paper on SLIT (20).

As far as the treatment duration is concerned, it is generally recommended in consensus documents that AIT is continued for 3–5 years (19,20). The available literature suggests that such duration maintains the efficacy for allergic symptoms for at least an equivalent period of time, with no significant differences seen between 3 and 5 years. However, studies with more prolonged follow-up periods are needed to investigate the persistence of the clinical benefit over the longer term (47).

Conclusions

In the last decade, AIT achieved significant advances in terms of understanding the optimal ways of its application as well as its mechanisms of action. In particular, SLIT was found to be a safe and effective therapeutic alternative to SCIT, being easier to implement and to continue for the recommended duration. The rigorous trials performed with the SLIT preparations in tablet form on large populations of pollen-allergic patients, in order to fulfil the requirements for registering the products as pharmaceutical therapies, provided physicians and patients with a treatment whose efficacy had been confirmed with the highest level of scientific evidence and improved the credibility of

AIT for the entire medical field. Further advances are needed in AIT with respect to appropriate patient selection and dosage for administration, as well as the quality and composition of the allergen extracts. These latter aspects involve at least the expression of the content of major allergens in microgram amounts, as required by SLIT guidelines and position papers.

Conflicts of interest

Franco Frati and Ilaria Dell'Albani are employees of Stallergenes Italy. Cristoforo Incorvaia is a scientific consultant for Stallergenes Italy.

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