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Allergen Immunotherapy: Current State and Ways Forward

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Abstract

Allergen specific Immunotherapy (AIT), introduced more than one century ago, is the only allergen-oriented biological response modifier that redirects in a complex way the mode of response to antigens of the immune system. The traditional route of administration had remained for decades the subcutaneous one. In the last 30 years the sublingual administration was introduced and accepted. Nowadays, there are numerous large regulatory trials (mainly with sublingual tablets) confirming the efficacy and safety of this route for the more relevant allergens. The efficacy and safety of sublingual AIT was also consistently demonstrated in asthma, and the treatment is now included as possible adjunct in asthma guidelines. Obviously, a proper standardization of the products is mandatory. The component resolved diagnosis approach, allowed to better refine the prescription and the selection of candidate patients for AIT. In the next future, new administration routes are expected (epicutaneous, intralymphatic), together with the use of adjuvants. Also, the role of oral or sublingual desensitization for food allergy is currently emerging.

Keywords: Allergen immunotherapy; Subcutaneous immunotherapy; Sublingual immunotherapy; Efficacy; Safety

Comment

Allergen specific Immunotherapy (AIT) was introduced in clinical practice more than one century ago, with the supposed aim of "vaccinating" against some hypothetical "aerogenic toxins". Despite the rationale was wrong (the IgE subclass was discovered 50 years later), the procedure resulted clinically effective and therefore its use rapidly spread. Subcutaneous Injection (SCIT) remained the only mode of administration for more than 70 years, although new modalities were time to time proposed, with the aim of improving the safety and convenience. Among the various routes proposed, the Sublingual one (SLIT) rapidly gained credibility, so that it was accepted as a viable alternative to SCIT in all official documents and guidelines [1]. In general, the clinical efficacy of SLIT and SCIT are equivalent, although SLIT still displays a more favorable safety profile [2].

To date, the practice of SCIT is sufficiently standardized, as testified by position papers and practice parameters [3-7]. On the other hand, SLIT can be administered as drops, monodose vials or tablets, with variable timings and doses depending on the manufacturer. In the last decade, highly standardized products in tablets (grass, mite, and ragweed) were approved as drugs by EMA and FDA. The aim of AIT is to interfere with the immune response to the offending allergen, thus inducing a tolerance that results in a reduction of symptoms and medication intake upon natural exposure to the allergen itself [8]. SCIT usually consists of an up-dosing phase (with gradually increasing doses of the allergen) followed by a maintenance phase, were the maximum or optimal dose is given at regular intervals (usually monthly) for 3-5 years. With SLIT, due to the favorable safety profile, the up-dosing phase is absent or very short, and the maintenance given on daily basis.

It is true that SLIT represented an important step forward in AIT, but also it probably prompted more detailed investigations, leading to novel possible therapeutic approaches. Of note, some randomized controlled trials specifically designed for asthma were performed with AIT [9-11]. Asthma ever remained an uncertainty for the use of AIT, since the majority of the studies were conducted in rhinitis, without formal objective assessments for asthma, and asthma was considered a risk factor for adverse events with AIT. The new trials, indeed, showed that AIT is clinically effective also on asthma symptoms and can reduce the exacerbation rate and the consumption of controller medications, including oral corticosteroids [12]. In addition, an extensive review of literature suggested that asthma is not an absolute contraindication to the use of AIT [13]. For this reasons, SLIT have been recently accepted as an adjunct treatment in the GINA document [14]. The more recently conducted double blind placebo controlled trial confirmed the preventative effect and the reduction of the risk of asthma onset in children with allergic rhinitis [15].

The more and more detailed immunological and clinical knowledge on allergic disorders [16] provided the opportunity for new approaches. For instance, new modalities of administration were proposed, namely intralymphatic and epicutaneous. Those routes of administration seem to achieve a clinical efficacy similar to the traditional SLIT and SCIT routes, with lower doses of allergen(s) and/or reduced side effects [17,18]. The use of AIT was also proposed for other atopic disorders such as atopic dermatitis, although the results in such condition are promising, but not conclusive [19].

The other relevant and promising aspect of AIT (in this case "oral desensitization") is food allergy. In fact, numerous controlled trials showed that the administration of gradually ascending doses of the offending food (milk, egg, peanut), can achieve a full tolerance to the food itself [20]. It is still not clear if this procedure can induce a permanent desensitization, or if the achieved tolerance must be maintained with a regular assumption of the food. The use of desensitization (either oral or sublingual) is nonetheless confined to

research, and it is recommended that this practice must be performed only under medical supervision, due to the occurrence (about 20%) of severe adverse reactions [21].

Finally, the introduction of molecular diagnosis instruments allowed to better refine the prescription of AIT [22,23]. In this regard, the use of a "tailored" AIT, considering only the relevant allergenic molecules still remains a new horizon, despite the high costs.

AIT, in any field of clinical application (i.e., when the pathogenic mechanism is well known and the allergen is clearly identified) achieved surprising advancements in the last decade. The use of the component resolved diagnosis model, the bio-engineering techniques and, especially the use of large-population based (often with a dose-finding design) trials, allowed to better define the indications and limitations of this therapeutic approach. This keeps true in particular for SLIT, which still remains the most investigated route of administration, also due the introduction of the tablet formulation. The use of SLIT or "oral desensitization", in its various forms and procedures, also remain an intriguing field of research for food allergy. Finally, it must be highlighted, that it is currently not possible, and not scientifically correct, to consider the clinical effects of AIT as a general "class effect", but the efficacy itself needs to be clearly demonstrated and documented for each single product, with a well-defined dose [24], so that AIT can optimally approach the model of precision medicine [25], although an univocal predictive biomarker of efficacy is still lacking.

Conclusion

After decades of empirical use, AIT has recently gained a robust credibility, especially in its sublingual administration. There are numerous substantial proofs of its efficacy and safety (including allergic asthma), with standardized products, that are approved by the main regulatory agencies. The possibility of refine the prescription by the molecular diagnosis procedures, and the detailed knowledge of the mechanisms of action, makes AIT a good example of precision medicine, leaving also open horizons for the improvement of this kind of immunological treatment. Finally, some methodological aspects need to be addressed to make the "big trials" comparable, at least in term of outcome, inclusion criteria and data management [26].

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