

SPECIFIC IMMUNOTHERAPY: STILL YOUNG AFTER ONE CENTURY

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Specific immunotherapy (SIT) is one of the oldest treatments in the recent history of medicine. It was introduced in clinical practice about one century ago (1). Of note, at the beginning it was based on a completely wrong hypothesis: the "vaccination against airborne toxins". In the mind of the first proposers, SIT would have acted exactly as all vaccinations against infectious agents, inducing a tolerance. It has to be kept in mind that at the beginning of the XX century immunology was at its earliest stage and it was still a minor part of the branch of infectious diseases. Despite the wrong premise, the subcutaneous administration of gradually increasing amounts of pollens immediately proved effective in curing the symptoms of hayfever, and rapidly become an accepted therapeutic option. The pathophysiology of the allergic reaction began to be explained 50 years later with the discovery of the IgE immunoglobulins by Ishizaka (2) and Johansson. At that time, SIT was anyway commonly used to treat hayfever and house-dust related respiratory allergy. The first double blind placebo controlled evaluation of the efficacy of SIT was made in the sixties by Lowell and Franklin (3). Starting from that seminal study, scientific evidence for the clinical and immunological effects of SIT, rapidly accumulated. In 1986 the British Council for the safety of medicines (4) reported 26 well documented deaths due to SIT, and raised serious concerns on the risk to benefit ratio of subcutaneous SIT in respiratory allergy, also because inhaled steroids had become available at a low cost. Starting from that point it became clear that indications and practical aspects of SIT had to be critically revised. Moreover, the increased interest on safety aspects, rapidly promoted the investigation on routes of administration different from the subcutaneous one: the oral, sublingual and intranasal ones (for review see 5).

Since the first randomized controlled trial (6), the sublingual immunotherapy (SLIT) appeared to be a promising candidate, because of the good risk to benefit ratio. Nowadays, 29 placebo controlled trials are available, incontrovertibly showing that SLIT is effective in respiratory allergy. A meta analysis study has recently provided a formal confirmation of the efficacy of SLIT, at least in rhinitis (7), and some post-marketing surveys have shown that the rate of side effects with SLIT is low, and severe adverse events never occur. Thus, SLIT represents a real step forward in the management of respiratory allergy, although some aspects (preventive effect, indications in children, mechanisms of action), require further work.

In the last 20 years the overall view of respiratory allergy and underlying immunological mechanisms has deeply changed and evolved. It has become progressively clear that allergy is much more than IgE and mast cells. For instance, numerous factors (even during foetal life) contribute to the development of the atopic status, and to the subsequent appearance of the clinical disease. In addition, after the allergen-IgE interaction has taken place, a complex inflammatory network is established, sometimes leading to chronic inflammation and tissue remodeling. Many of the components of the allergic reaction and inflammation and their role have been identified and described. In parallel, the immunological and biochemical techniques have made possible to synthesize engineered molecules, specific antibodies and sometimes therapeutic gene constructs. Thus, starting from the middle eighties there was a dramatic acceleration of the research in immunotherapy. Some of the results of that research are exemplified by the adjuvanted allergens (8), the liposome-encapsulated vaccines (9), and the association of SIT with anti-IgE antibodies (10). New experimental approaches were established,

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to maintain the immunogenicity of the vaccine without the capacity to bind allergen-specific IgE. Examples of this approach are recombinant and genetically modified allergens, and allergenic peptides (11, 12). The most attractive field of research in immunotherapy is the genic approach, which includes the use of allergens conjugated with DNA immunostimulatory sequences. The first exploratory study performed in humans with DNA-conjugated ragweed allergen (13) provided positive results and disclosed new horizons in the field. The genic approach also includes the administration of cDNA plasmids encoding for a given allergen (14). This latter approach seems, however, to belong to the very far future.

In conclusion, the history of SIT is one century long, but SIT is far from being an historical treatment. On the contrary it is one of the most intriguing and fruitful research arguments, as testified by the impressive number of articles dedicated to the new immunotherapeutic approaches (15), some of them also becoming a clinical reality.

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