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EDITORIAL

Sublingual immunotherapy is safe in children, but the challenge is how to increase its efficiency?

At the beginning of the twentieth century, in London, Leonard Noon[1] gave injections of pollen extracts to patients with hay fever, following the same strategy that was applied at that time to prevent infectious diseases with vaccines.[2] More than a century has elapsed and many studies have repeatedly proved the benefits of the immunotherapy (IT) for allergic diseases, compared with placebo, having the important advantage, over drug therapy, of inducing tolerance for up to three to five years after discontinuation of therapy. Moreover, several reports have shown that the administration of IT to children with allergic rhinitis delays or prevents the progression to asthma,[3] and so was considered in 1998 by the World Health Organization as the only treatment with the ability to modify the natural course of allergic disease.[4] In spite of these benefits, the traditional IT, administered by subcutaneous via (SCIT) continues to be a matter of permanent controversy, mainly among non-allergist physicians. Maybe the main reason for the persistence of this discussion throughout a century was that after many years of excellent results, the therapeutic mechanism of IT remains unclear. A persistent fear of SCIT is the risk of severe adverse effects, with the bad experience of some patients who died every year due to anaphylactic reactions. Other negative conditions of lesser but significant importance are the discomfort of subcutaneous injections, and the inconvenience of regular visits to the allergist's office, two conditions that tend to restrict a wider use of SCIT.

The introduction of IT administered by sublingual via (SLIT) two decades ago was soon very well admitted in paediatric clinical practice, assuming it has higher safety than SCIT. The comparison of SCIT and SLIT procedures became an unavoidable issue.[5,6] Nevertheless, the main question about SLIT remains unanswered, at least with respect to paediatric patients: is SLIT safer than SCIT at the level dose of a similar efficacy? At least SLIT seems to have one clear advantage, the facility of self-administration at home, avoiding, total or partially, the presence of a physician or health-care professional. In the last decade, many clinical trials in adult or paediatric patients have been published, although the wide spectrum of indications of IT; different preparations; dose schedules; duration of therapy; type of sensitisation make it difficult to draw firm conclusions about the efficacy of SLIT. This problem is even greater when SLIT is administered to children of different ages. Therefore, more paediatric trials need to be performed and for a longer period of time, especially focused on the treatment of house dust mite sensitisation, which has been studied less than rhinitis caused by pollen.

In the current issue of Allergologia et Immunopathologia, Ferres et al.[7] publish a retrospective observational study performed in 78 children (66 completed the study) with a mean age of 11.0 years. They have allergic rhinitis with a confirmed dust-mite sensitisation. Most patients (69%) associated asthma, which according to the GINA classification was intermittent (51%) or mild to moderate persistent asthma (49%). All children received high-dose SLIT with either a conventional (11 days) or an ultra-rush (1 day) initial phase, followed by maintenance treatment during a variable period from two to 52 months. The aim of the study was to evaluate the efficacy and the safety of a high-dose SLIT to dust-mite sensitisation in children. A total of 18 patients (23.1%) presented adverse reactions; in most cases the symptoms were mild and local, such as irritation, oedema or small ulcers on the tongue. These reactions were significantly more frequent in patients who received the initial ultra-rush regimen. Five children (6.4%) showed gastrointestinal reactions and only one patient suffered a systemic reaction, with mild headache. None of the cases showed anaphylactic reaction.

The efficacy of the SLIT treatment was assessed according to the clinical data recorded at 6, 12, 24, 36, and 48 months. The severity of rhinitis was quantified by the visual analogue scale (VAS), and by a rhinitis medication score (RMCS). Similar methods were used for the assessment of asthma in those patients who suffered from the disease. Patient evolution of VAS score revealed a high significant improvement in the first six months after starting SLIT treatment and this was maintained throughout the four-year follow-up. The use of medications also decreased during the first six months of SLIT and remained very low during the follow-up period. Moreover, the proportion of patients free of any pharmacological therapy for rhinitis increased over

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time, especially at the moment of the first visit. The good results were also obtained in those patients with rhinitis plus asthma.

The results reported by Ferres et al. are consistent with the evidence previously published by other authors[8,9] that a high-dose SLIT for mite-dust is well tolerated in children and could be an effective treatment for patients with both rhinitis and asthma.

Several meta-analyses have been published so far which have confirmed the efficacy of SLIT in randomised studies,[10–15] nevertheless Nieto et al.[16] assessed the consistency and the robustness of their conclusions and concluded that the published meta-analyses do not provide enough evidence to support the current use of this kind of immunotherapy as a first-line treatment for allergic diseases. The consistency of this conclusion might be even stronger giving that the beneficial effects tend to be overestimated in clinical research, due to the lower impact of negative results. On the other hand, the evaluation of a meta-analysis should always be done with caution, because the approach should be uniform for all studies, and this is not the case in SLIT trials. Moreover, the negative results found by other authors might be related to a low total dose of allergen administered.

There is increased evidence that Treg cells and a shift from Th2 to Th1 cytokine types play a pivotal role in SCIT. It means that IT by subcutaneous via ''drives'' the erroneous atopic response against allergen.[17] The immunological mechanism of SLIT has been a matter of interesting studies and, at first glance, it might be partially different from SCIT.[18] The oral cavity belongs to the mucosal immune system, where the induction of tolerance is the predominant response against a variety of antigens. The distribution of dendritic cells (DC) within the mouth mucosa is not homogeneous and its degree maturation may vary among them.[19] Langerhans cells represent the predominant DC in human oral mucosa, whereas mature plasmocytoid DC, are virtually absent.[20] After antigen capture, the antigen presenting cells from the oral mucosa differentiate to semimature DC, Langerhans cells, and then to mature DC that migrate to the regional lymph node. Immature and semimature DC are tolerogenic, whereas fully mature DC may have immunogenic phenotype promoting IFNg-producing T cells.[21] A relevant issue is the relative low number of Langerhans cells within the sublingual region; this has led some authors to search for an alternative site of allergen application, such as the vestibular region.[22]

An interesting perspective for the future of SLIT might be to promote the expansion of Treg with adjuvants.[23] Several well-known factors such as retinoic acid, vitamin D, rapamycin, glucocorticoids and lactobacillus have been identified in mice studies and are waiting for their use in humans.[24–29] More than 80 years of experience and thousands of treatments have been needed to optimise the SCIT technology and dosage. Now, in spite of the knowledge on mucosal immunology achieved, many more years of research will be needed to improve the SLIT methodology with adequate adaptation to paediatric conditions.

In general terms, SLIT may be considered as a safe therapy in paediatrics,[30] although high-dose and long courses might be needed in order to reach good results.[31] Nevertheless, its efficiency needs to be improved in order to obtain similar results to subcutaneous administered immunotherapy.

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