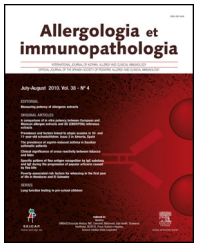
Allergol Immunopathol (Madr). 2013;41(4):213–215

Allergologia et immunopathologia

www.elsevier.es/ai



EDITORIAL

Sublingual Immunotherapies: The more we know, the more we need to know

Sublingual Immunotherapy (SLIT), as a general term, comprises a large group of different medicinal products that share a common route of administration but have different formulation, allergen standardisation, doses and many other relevant differences, including their regulatory status. According to this last feature, the medicinal products included in SLIT, as a medicinal product class, can be loosely classified into three subgroups. The first subgroup includes the small minority that have proceeded through a standard drug development procedure and have obtained a Marketing Authorization according to the Directive 2001/83/EC as amended by the European regulatory agency (EMEA) like any other drug, i.e., the **standard drug Sublingual Immunotherapies**, which have the strongest evidence support based on large-scale randomised placebo-controlled clinical trials in adults and children and can be considered the elite of the SLIT class. The second subgroup includes the large majority of Sublingual Immunotherapies approved in European Countries by local Regulatory Agencies as immunological products manufactured by authorised immunological/pharmaceutical companies on a named-patient basis specifically for sublingual route administration, which we shall describe as the **Southern Europe Style Sublingual Immunotherapies**. The evidence supporting the efficacy and safety of the medicinal products included in this group is generally scarce on an individual basis, but, as a group, there are a good number of systematic reviews and a metaanalysis that support their clinical use.[1–3] In Scandinavian countries, allergen extracts have only been available as standard drugs for decades and no market exist for named-patients products, including SLIT.[4] The third group is the **USA Style sublingual off-label immunotherapies** which comprises the aqueous preparations formulated in most cases in the allergist office on a named-patient basis, often containing several different antigens, and approved only for subcutaneous administration but prescribed off-label, i.e., for a non-approved use, for sublingual administration.[4] In North America only the third subgroup of SLIT medicinal products are available for clinical use. This simple, straightforward classification may explain why the use of SLIT medicinal products is so different around the world. In USA, only 6–11% of allergists use SLIT,[4,5] whilst in Europe they represent approximately 45% of the total Specific Immunotherapy (SIT) prescribed, with large differences between countries: in northern Europe almost none and only standard drug SLIT. In Germany, it is 25% and in Southern Europe, up to 80%. Curiously, the standard drug SLIT subgroup is not among the most prescribed SLIT medicinal products, despite strong supporting evidence.[4]

In the current issue of *Allergologia et Immunopathologia*, Marogna et al. report the results of an interesting randomised but open-labelled clinical trial assessing the contribution of one of the medicinal products included in what I have called *Southern Europe Style Sublingual Immunotherapies* (i.e., a medicinal product approved by Italian Regulatory Agency on a named-patient basis, although with a standard tablet formulation containing a carbamylated monomerid allergoid from birch pollen[6] [Lais®, Lofarma S.p.A., Milan, Italy]) to the achievement of asthma control in adult patients with mild persistent seasonal asthma monosensitised to birch pollen not controlled during the run-in season by a step-2 standard treatment with budesonide 400 mcg inhaled daily.[7] The study design has some remarkable key features: it is a long-term clinical trial prospectively comprising four seasons, one for run-in and three for active treatment; the investigational treatment (adding Lais® to the step-2 budesonide dose that had previously failed to control asthma) is put in direct comparison to standard step-3 treatment, i.e. doubling or quadrupling the budesonide dose or adding a second controller drug, montelukast, to the previous step-2 budesonide dose. In this way, the authors have directly compared adding the SLIT medicinal product as an additional controller with three other common increases in drug treatment. The primary end-point is a solid, well validated and clinically relevant one, the mean monthly Asthma Control Test results, with some other relevant secondary end-points, including spirometry results. The final results are outstanding: the group of patients ($n = 21$) that received three pre-coseasonal courses of Lais® along with budesonide 400 mcg did exceedingly better than the other three groups ($n = 21$, respectively). The mean (±SD) ACT value after three seasons of treatment

0301-0546/$ - see front matter
http://dx.doi.org/10.1016/j.aller.2013.06.001

was 24 ± 0.2, reaching almost the maximum value (25), and leaving almost no room for further improvement, compared with 17.2 to 18.4 in the other groups. Mean FEV1 raised from a basal predicted value of 85% to an excellent 103% after the third treatment season compared to 90–96% in the other groups. These results suggests that adding Lais® to adult asthmatic patients monosensitised to birch pollen who are not adequately controlled by standard step-2 treatment with budesonide 400 mcg daily is superior to standard alternatives of increasing the budesonide dose or adding a second controller. These results are very relevant because they support the inclusion of the experimental medicinal product (Lais®) in the standard step-wise pharmacological treatment in this selected adult population, who, incidentally, were selected by traditional allergic evaluation with prick test and serum specific IgE against birch pollen and not using molecular diagnostic procedures, as in most if not all clinical trials on SIT.

However, this randomised clinical trial has some important weaknesses. The lack of blinding may certainly be a source of bias, partially corrected by an appropriate randomisation procedure. The open label nature of the study, euphemistically referred to by the authors as a ''real-life randomised trial'' may be an obstacle to include this trial in some high quality metaanalysis, but not all, which usually consider only double-blind randomised clinical trials of high quality. For instance, using the Jadad scoring system (from 0 to 5), only two points would be obtained by this trial. Also, the European Guidelines for the clinical development of products for specific immunotherapy for the treatment of allergic diseases[8] establish a double-blind placebo-controlled design to obtain evidence of efficacy and safety, even in children,[9] for marketing authorisation purposes. ''Real life'' designs, i.e. open-labelled clinical trials, are only justified when a very large population is needed to obtain valid conclusions and blinding or placebo use is particularly difficult, which is not the case. As in most of the *Southern Europe Style SLIT clinical trials*, the number of participants is rather low (21 per treatment group), consistently with the one centre nature of the clinical trial. Compared with multicentre randomised double-blind placebo-controlled clinical trials from development programmes of *standard drug SLIT*, such as that recently published by Creticos et al., ($n = 784$, double-blind, placebo-controlled in patients with ragweed allergy)[10] the number of participants of the study of Marogna et al. seem low. However, due to the large beneficial effect of the experimental treatment, the difference between the experimental group and control groups reached statistical significance.

It is a common statement that the efficacy of SLIT in allergic asthma is well supported by systematic reviews and metaanalysis. So, do we need more clinical trials on the subject like the one we are commenting on? The answer is yes, we certainly do. The title of a recently published editorial in the *Journal of the American Medical Association* commenting on one of the latest metaanalyses on the subject[1] is quite clear in this respect: Is sublingual immunotherapy Ready for Use in the United States?[11] And the conclusion is: no, it is not. However, from the European point of view, SLIT is ready for use and we have been using it lawfully for many years. But we do need to know more about *each medicinal product* of this class and keep on advancing to the ideal situation in which *each SLIT medicinal product* has a full development programme supporting its approval, including their Pediatric Investigation Plans for children[12] and complete safety records.[13] This is why I heartily welcome the paper by Marogna et al. and encourage immunotherapy companies to further develop their SLIT medicinal products following their Regulatory Agencies guidelines and not relying on data obtained with other SLIT medicinal products all mixed up in heterogeneous metaanalyses and systematic revisions. That is why I keep on using the term Sublingual Immunotherapies (in plural). The time for standard individual approval and beyond has come.[14]

References

1. Lin SY, Erekosima N, Kim J, Ramanathan M, Suárez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma. A systematic review. JAMA. 2013;309:1278–88.
2. Larenas-Linnemann D, Blaiss M, Van Bever HP, Compalati E, Baena-Cagnani CE. Pediatric sublingual immunotherapy efficacy: evidence analysis 2009–2012. Ann Allergy Asthma Immunol. 2013;110:402–15.
3. Álvaro M, Sancha J, Larramona H, Lucas JM, Mesa M, Tabar AI, et al. Allergen-specific immunotherapy: update on immunological mechanisms. Allergol Immunopathol (Madrid). 2013 http://dx.doi.org/10.1016/j.aller.2012.07.018
4. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. Ann Allergy Asthma Immunol. 2009;103:451–60.
5. Sikora JM, Tankersley MS. Perception and practice of sublingual immunotherapy among practicing allergists in the United States: a follow-up survey. Ann Allergy Asthma Immunol. 2013;110:194–7.
6. Mösges R, Ritter B, Kayoko G, Passali D, Allekotte S. Carbamylated monomeric allergoids as a therapeutic option for sublingual immunotherapy of dust mite and grass pollen induced allergic rhinoconjunctivitis: a systematic review of published trials with a metaanalysis of treatment using Lais® tablets. Acta Dermatoven APA. 2010;19:3–10.
7. Marogna M, Braidi C, Bruno ME, Colombo C, Colombo F, Massolo A, et al. The contribution of sublingual immunotherapy to the achievement of control in birch-related mild persistent asthma: a real life randomized trial. Allergol Immunopathol (Madrid). 2013;41:216–24.
8. Guidelines on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf; [accessed on 09.06.13].
9. EMA/PDCO Standard Paediatric Investigation plan for Allergen Products for Specific Immunotherapy. Revision 3. EMA/PDCO/737605/200909. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500015814.pdf; [accessed on 09.06.13].
10. Creticos PS, Maloney J, Bernstein DI, Casale T, Kaur A, Fisher R, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European Adults. J Allergy Clin Immunol. 2013;131:1342–9.
11. Nelson HS. Is sublingual immunotherapy ready for use in the United States? JAMA. 2013;309:1297–8.
12. Calderon MA, van Wijk RG, Eichler I, Maricardi PM, Varga EM, Kopp MV, et al. Perspectives on allergen-specific

immunotherapy in childhood: an EAACI position statement. Pediatr Allergy Immunol. 2012;23:300–6.
13. Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox L, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. J Allergy Clin Immunol. 2013 http://dx.doi.org/10.1016/j.jaci.2013.03.039
14. Calderón MA, Casale TB, Togias A, Bousquet J, Durham S, Demoly P. From meta-analysis to registration and beyond. J Allergy Clin Immunol. 2011;127:30–8.

Antonio Martínez-Gimeno
Department of Pediatrics, Hospital Virgen de la Salud, Toledo, Spain
E-mail address: amgimeno@gmail.com