EDITORIAL

NEW ADMINISTRATION ROUTES IN IMMUNOTHERAPY

The most recent publication of the World Health Organization's Expert Committee, supported by the various European, American and Japanese Academies and Societies of allergy, asthma and immunology, has finally settled the long-running controversy on the efficacy and risks of immunotherapy (1). This publication has served to support the cumulative experience of many specialists (2), who in their daily practice have witnessed the efficacy of this therapy as well as its minimal risks, which are similar to those of other drugs (AAS, beta-lactams, anesthetics) (3-5).

Without doubt, early administration of immunotherapy in allergic asthma, after identification of the allergen, is the greatest guarantee of favorable evolution, the best results having been obtained in this condition (6, 7). Allergic rhinitis is also a specific indication for immunotherapy, with acceptable results. However, it is well known that many asthmatics simultaneously present symptoms of rhinitis and that although treatment produces considerable improvement in asthmatic symptoms, rhinitis symptoms persist, which puts in doubt the efficacy of subcutaneous immunotherapy in the treatment of patients with rhinitis.

The most common route of administration is subcutaneous*. Consequently, experience is greatest with this route and its mechanism of action is becoming increasingly better understood (8). However, the most serious adverse reactions have also been produced with this form of immunotherapy. For this reason, as well as to facilitate and make this route of administration more acceptable, above all in children, new forms of immunotherapy, such as* oral *and* sublingual*, have been developed. Of these two routes, that which is preferentially being used is the sublingual route, which offers the possibility of either swallowing the extract, after keeping it under the tongue for about two minutes, or of spitting it out to avoid the oral route which can produce gastrointestinal adverse effects (9). Nevertheless, in practice, sublingual immunotherapy may give way to oral immunotherapy, given the difficulty of maintaining the extract under the tongue for the required length of time, especially in children. Most recent publications on the use of the sublingual immunotherapy report that investigators prefer it because it seems to be more effective. In this edition of* Allergologia et Immunopathologia*, C. Valle, et al. report a controlled study of the efficacy of sublingual immunotherapy with Ambrosia pollen (10).*

A fair amount is currently known on the systemic mechanism of action through which the beneficial effects of the three routes of administration already discussed are obtained, although studies have concentrated on the most commonly used route, the subcutaneous route, believing that the other two act through a mechanism that must in part be similar. However, doubts have been raised concerning the efficacy of these routes when the clinical problem is highly localized, as when the patient presents symptoms

only of rhinitis or, above all, of conjunctivitis, given that it is possible that the changes in immune response caused by the subcutaneous vaccine do not reach such highly localized mucosal areas equally. For this reason, new routes are not surprisingly being sought, such as the topical application on the affected mucosa. Of these routes, topical nasal immunotherapy was the first to be introduced and is that in which experience is greatest (11). This therapy produced good results and its local mechanisms of action seem to be fairly clear (12, 13).

Few trials have been performed on direct administration by bronchial inhalation*, because adverse reactions were soon observed, especially bronchospasm, as if in response to bronchial provocation, although acceptable results were obtained in other studies (14, 15).*

Also in this edition of Allergologia et Immunopathologia*, Núñez and Cuesta (16) propose a new topical route, local* conjunctival *immunotherapy, for the treatment of patients in whom conjunctivitis is the only allergic manifestation. The difficulties of confirming the diagnosis of any of the variants of ocular allergic are well known (17) since specific IgE in the serum of approximately half of all patients cannot be demonstrated and the results of skin tests are also negative. In contrast, in conjunctival mucosa and in tears, indicators of an allergic inflammatory reaction can be detected (18, 19) hence the advisability of performing conjunctival provocation tests to confirm the diagnosis. The use of this new route of administration proposed by these Argentinian authors, whose first results are promising, is very suggestive, given that etiological treatment of these processes through subcutaneous immunotherapy is not very effective; moreover, the results are as uncertain as the diagnosis, since the positive results published generally correspond to patients with rhino-conjunctivitis and consequently the clinical problem is different. Obviously, greater experience is needed with this route as its safety and efficacy must be demonstrated by establishing treatment protocols: dose, guidelines, type and quality of the extracts, time of treatment, etc. In addition, its mechanism of action must be determined.*

F. Muñoz-López

REFERENCES

1. WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Allergy 1998;44 Supl: 53.
2. Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an update systematic review. Allergy 1999;54:1022-41.
3. Businco L, Zannino L, Cantan L. Systemic reactions to specific immunotherapy in children with respiratory allergy: a prospective study. Pediat Allergy Immunol 1995;6:44-7.
4. Luigi A, Senna G, Mezzelani P, Pappalardo G. Safety of specific immunotherapy: a retrospective study. J Invest Allergol Clin Immunol 1994;4/5:250-4.
5. Rogala B. Risk and safety of immunotherapy. Allergy 1998;53:473-6.
6. Hedlin G, Wille S, Browaldh L, Hildebrand H, Holmgren D, Lindfors A, et al. Immunotherapy in children with allergic asthma: effect on bronchial hyperreactivity and pharmacotherapy. J Allergy Clin Immunol 1999;103/4:609-14.

7. Creticos PS. The consideration of immunotherapy in the treatment of allergic asthma. J Allergy Clin Immunol 2000;105/2(2):S559-74.
8. Akdis CA, Blazer K. Mechanisms of allergen-specific immunotherapy. Allergy 2000;55:522-30.
9. Wheeler AW, Drachenberg KJ. New routes and formulations for allergen-specific immunotherapy. Allergy 1997;52:602-12.
10. Valle, C, Bazzi S, Berra D, Sillano V, Puccinelli P, Parmiani S. Effects of sublingual immunotherapy in patients sensitised to Ambrosia. An open controlled study. Allergol et Immunopathol 2000;28:310-6.
11. Bonini S (Guest editor). Local nasal immunotherapy. Allergy 1997;33 Supl 52:5-44.
12. Martín Mateos MA, Monferrer R, Muñoz-López F. Topical nasal immunotherapy. Immunologic response of IgE in nasal secretion after immunotherapy with Dermatophagoides pteronyssinus. Allergol et Immunopathol 1990;18:223-8.
13. Passalacqua G, Albano M, Ruffoni S, et al. Nasal immunotherapy to Parietaria: evidence of reduction of local allergic inflamation. Am J Respir Crit Care Med 1995;152:461-6.
14. Tari MG, Mancino M, Monti G. Immunotherapy by inhalation of allergen in powder in house dust allergy asthma. A double-blind study. J Invest Allergol Clin Immunol 1992;2:59-67.
15. Passalacqua G, Bagnasco M, Mariani G, Falangiani P, Canonica GW. Local immunotherapy: pharmacokinetics and efficacy. Allergy 1998;53:477-84.
16. Núñez JA, Cuesta U. Local conjunctival immunotherapy: the effect of dermatophagoides pteronyssinus local immunotherapy on conjuntival provocation test in patients with allergic conjuntivitis. Allergol et Immunopathol 2000;28:301-6.
17. Abelson MB, George MA, Garofalo C. Differential diagnosis of ocular allergic disorders. Ann Allergy 1993;70:95-109.
18. Bonini Se, Bonini St. Vernal keratoconjunctivitis. A model of Th2 disease. ACI International 1998;10/3:88-91.
19. Barney NP, Cook JL, Stahl JL, Sukow KA, Graziano FM. Human conjuntival mast cells (HCMC) release and express message for TNF-alpha in response to anti-IgE challenge in a time and dose dependent manner. J Allergy Clin Immunol 1999;103/1(part 2):S41.