

Clinical efficacy and safety of local nasal immunotherapy

Andri L, Senna GE, Dama AR. Clinical efficacy and safety of local nasal immunotherapy.
Allergy 1997; 52(suppl 33): 36–39. © Munksgaard 1997.

L. Andri, G. E. Senna, A. R. Dama

Servizio Autonomo di Allergologia, Istituti
Ospitalieri di Verona, Piazzale Stefani, 1,
37126 Verona, Italy

Local nasal immunotherapy represents an alternative route of allergen administration. It was proposed to overcome the risk of systemic reactions rarely reported during the traditional subcutaneous immunotherapy. Some studies carried out in the past generally showed good efficacy but poor tolerability. The aqueous extracts mostly used in these studies carry some drawbacks such as the volume effect, self-digestion and the difficulty of administering reproducible dosages. The recent availability of allergen extracts in powder form has led to better stability and standardization. The studies carried out with these freeze-dried allergens showed clinical efficacy and good tolerability in perennial (mite, cat) and seasonal (grass, birch, *Parietaria*) allergic rhinitis. According to these findings this new local nasal immunotherapy with extract in powder form represents a suitable alternative to the traditional immunotherapy in the treatment of allergic rhinitis.

Key words: local nasal immunotherapy; hyposensitization; allergic rhinitis; hay fever; pollinosis.

Prof. Luigi Andri
Servizio Autonomo di Allergologia
Ospedale Civile Maggiore
Piazzale Stefani 1
37126 Verona
Italy
Tel. & fax: 39-45-8072048

Specific immunotherapy is the mainstay treatment for allergic respiratory diseases. Its efficacy has been proved both in asthma (1) and in rhinitis (2); however, because this treatment is used in non-life-threatening conditions, such as allergic rhinitis, consideration of its benefit/risk ratio is of great importance. Traditional subcutaneous immunotherapy presents some disadvantages, including cost, compliance (need of frequent medical calls) and, above all, rare severe systemic reactions (3). To overcome these problems alternative routes of allergen administration have recently been evaluated.

Oral and sublingual immunotherapy have been widely evaluated. They have been proved to be well tolerated, but the clinical results of controlled trials are conflicting. Better results are reported in young people and in birch pollinosis, while less or no efficacy has been demonstrated in adults and in grass pollinosis and in mite allergic rhinitis (4, 5).

Local nasal immunotherapy

Clinical studies using aqueous extracts

Local nasal immunotherapy (LNIT) represents another alternative route of allergen administra-

tion. Its clinical efficacy has been suggested by the demonstration of loss of sensitivity to grass pollen allergens in patients repeatedly challenged intranasally with threshold doses of allergens by means of specific nasal challenges (6). After this encouraging experience some investigators have reported uncontrolled studies, confirming clinical efficacy of LNIT in allergic rhinitis (7, 8).

Later double-blind controlled studies evaluated LNIT as a treatment of seasonal allergic rhinitis due to grass and ragweed pollens. Even though the results of these studies are controversial, the following data are confirmed by the majority of authors:

- i) Most of these studies reported clinical efficacy of this treatment (9–12);
- ii) However, local discomfort due to the treatment mainly at high doses of unmodified extracts caused severe immediate nasal symptoms (9, 11–13). These local side effects could cause difficulties in performing double-blind trials, also reducing the compliance of this alternative form of immunotherapy;
- iii) A better tolerability with clinical efficacy has been demonstrated with the use of modified

- allergens (9–12, 14). These extracts, however, have been reported to be less clinically effective in comparison with aqueous extracts (9, 10);
- iv) According to traditional subcutaneous immunotherapy, the efficacy of LNIT is dose-dependent, low doses of extracts being clinically ineffective (15–17) and clinical efficacy also being allergen specific (17);
 - v) No systemic reactions have been reported in any study, confirming the safety of this treatment;
 - vi) Conflicting results were reported with regard to the modifications of specific nasal sensitivity induced by LNIT, decreased in two studies (18, 19) and increased or unchanged in another five studies (10, 15, 16, 20, 21);
 - vii) An increase of serum specific IgE antibodies (12, 15) and of secretory allergen specific IgG and IgA antibodies (10, 16, 20, 21) have been observed, but clinical and immunological findings did not correlate (10–12, 21, 22).

These different results may reflect differences in dosages, length of treatment, schedules and extracts used by the authors.

The main problem of this treatment was its tolerability, causing the same symptoms that the treatment intended to prevent (5). In these studies preparations consisted of aqueous allergen solutions and were administered into the nostril by squeeze bottles. Disadvantages of the aqueous preparation are poor stability due to the volume effect and self digestion. Allergenic molecules may be observed on the inner surface of the container. This phenomenon can cause considerable loss of allergenicity, especially in diluted solutions (22). This can be prevented by use of surfactants (e.g. tweens) or inert proteins (e.g. albumin) but false reactions may develop (23). Self digestion is a phenomenon due to the presence of proteolytic enzymes in the extract, which can denature allergens. Partial purification of allergenic extract can prevent this phenomenon, but may be unavoidable when the allergen is an enzyme itself. For example Der p 1, the main allergen in house dust mite *Dermatophagoides pteronyssinus*, is a cysteine protease (24, 25).

Another disadvantage with aqueous extracts is the difficulty of dosing a reproducible quantity of allergen. Metered dose inhalers are not used for allergenic products because of chemical incompatibility between the aqueous solution and propellant. One way to administer aqueous solutions is as a spray using a squeeze bottle. Unfortunately, there is poorly reproducible dosage, varying according to the pressure applied to the squeeze bottle.

Local nasal immunotherapy with extracts in powder form: clinical results

Further progress in local nasal immunotherapy is the introduction of allergen lyophilized in powder (partition value = 45 μ m) form resulting in better allergen stability and standardization. More recently, some controlled studies have been performed by means of these freeze-dried extracts in powder form, leading to the following conclusions:

- i) A significant reduction of symptom and medication scores and specific nasal sensitivity has been reported by the majority of authors (26–32);
- ii) No systemic side effects have been reported in any study;
- iii) No difference has been observed with regard to local side effects between placebo and actively treated patients (26–28, 30–32), showing better tolerability (33) in contrast to previous studies; in these studies premedication with low doses of sodium cromoglycate, negligible as a therapeutic measure, was also administered to reduce local discomfort;
- iv) Less impressive results were observed in birch pollinosis (34);
- v) An open control study has shown that LNIT is less effective than the traditional subcutaneous immunotherapy in mite allergic rhinitis (35). However, the small number of cases and the fact that statistical analysis lacked comparison with a control group did not allow us to draw definitive conclusions.
- vi) Several asthmatic attacks have been reported recently during the treatment of *Parietaria* allergic rhinitis (31).

Mechanisms of action

As, for traditional subcutaneous immunotherapy, the mechanism of LNIT is still unclear, some immunological modifications were observed during the treatment. An increase of specific secretory IgA and IgG was reported by several authors (9, 10, 14, 21, 22), but without any clinical and immunological correlation (9, 10, 21).

A systemic immunological action could be hypothesized by the increase of serum specific IgE, reported after the treatment with intranasal aqueous extract (9, 21) and by the relevant allergenic activity observed in animal models after intranasal treatment with allergen in powder form (36). Concerning this, it is useful to remember that nasal mucosa has been already utilized for administration of drugs with systemic action.

However, so far the induction of a local tolerance due to repeated nasal administration of high

dosages of allergen extracts has been demonstrated only in animal models (37). More recently an effect of LNIT on mediators release was observed, such as a reduction of histamine production during early response to the specific nasal provocation after treatment (38) and a decrease of IL1 and IL8 production in nasal lavage after treatment (18). Moreover, a first experimental evidence of an active effect of LNIT on local allergic inflammation was demonstrated by the significant reduction of eosinophilic and neutrophilic infiltration evoked by the specific nasal challenge after active treatment (32). A significant reduction of intercellular adhesion molecule-1 (ICAM 1) expression on epithelial cells after specific nasal challenge was also demonstrated by the same authors (32).

Conclusions

According to these results LNIT in powder form can be considered a suitable alternative to the traditional subcutaneous treatment in term of efficacy and safety in allergic rhinitis. The advantage of this hyposensitizing therapy, compared to the traditional treatment by subcutaneous injections, seems to be a significant safety, as no severe and systemic side effects occurred. The recent report of rare bronchospastic reactions during treatment may be due to concomitant pollen exposure (31). Clinical studies performed by a preseasonal schedule did not show any asthmatic side effect (27, 30, 32). The clinical result appears in a short period of time (generally a few months), resulting in a very low cost/benefit ratio. However, this non-injective (alternative) immunotherapy is indicated only for monosensitized subjects, while in patients with multiple sensitizations the use of two different extracts should result in more severe local discomfort.

Further investigations are needed to clarify the mechanisms of action, the best schedule and length of treatment, the duration of therapeutic effect after withdrawal of treatment, as well as the clinical efficacy in direct comparison to traditional parenteral immunotherapy.

References

1. Creticos PS. Immunotherapy in asthma. *J Allergy Clin Immunol* 1989;83:554-62.
2. Norman PS. Immunotherapy for nasal allergy. *J Allergy Clin Immunol* 1988;81:992-6.
3. Norman PS, Van Metre TE. The safety of allergenic immunotherapy. *J Allergy Clin Immunol* 1991;85:522-5.
4. Bjorksten B, Dewdney JM. Oral immunotherapy in allergy. Is it effective? *Clin Allergy* 1987;17:91-4.
5. Bjorksten B. Local immunotherapy is not documented for clinical use. *Allergy* 1994;49:299-301.
6. Taylor G, Shivalkar PR. Local nasal desensitization in allergic rhinitis. *Clin Allergy* 1972;2:125-36.
7. Deuschl H, Johansson SGO. Hyposensitization of patients with allergic rhinitis by intranasal administration of chemically modified grass pollen allergen. *Acta Allergol* 1977;32:248-62.
8. Metha SB, Smith JM. Nasal hyposensitization and hay fever. *Clin Allergy* 1975;5:279-86.
9. Georgitis JW, Reisman RE, Clayton WF, Mueller U, Wypych JI, Arbesman CE. Local nasal immunotherapy for grass allergic rhinitis. *J Allergy Clin Immunol* 1983;71:71-6.
10. Georgitis JW, Nickelsen JA, Wypych JI, Barde SH, Clayton WF, Reisman RE. Local nasal immunotherapy with high doses polymerized ragweed extract. *Int Archs Allergy Appl Immunol* 1986;81:170-3.
11. Nickelsen JA, Goldstein S, Mueller U, Wypych J, Reisman RE, Arbesman CE. Local nasal immunotherapy for ragweed allergic rhinitis. I°. Clinical response. *J Allergy Clin Immunol* 1981;68:33-40.
12. Nickelsen JA, Goldstein S, Mueller U, Wypych J, Reisman RE, Arbesman CE. Local nasal immunotherapy for ragweed allergic rhinitis. III° A second year of treatment. *Clin Allergy* 1983;13:509-19.
13. Welsh W, Zimmerman EM, Yunginger JW, Kern EB, Gleich GJ. Preseasonal intranasal immunotherapy with nebulized short ragweed extract. *J Allergy Clin Immunol* 1981;67:237-42.
14. Johansson SGO, Deuschl H, Zetterstrom O. The use of glutaraldehyde modified timothy grass pollen extract in nasal hyposensitization treatment of hay fever. *Int Archs Allergy Appl Immunol* 1979;50:447-60.
15. Georgitis JW, Nickelsen JA, Wypych JI, Kane JH, Reisman RE. Local nasal immunotherapy: efficacy of low dose aqueous extract. *J Allergy Clin Immunol* 1985;75:496-500.
16. McLean JA, Mathews KP, Bayne NK, Brayton PR, Solomon WR. A controlled study of intranasal immunotherapy with short ragweed extract. *J Allergy Clin Immunol* 1980;65:191.
17. Welsh PW, Butterfield JH, Yunginger JW, Agarwal MK, Gleich GJ. Allergen-controlled study of intranasal immunotherapy for ragweed hay fever. *J Allergy Clin Immunol* 1983;71:454-60.
18. Kanz JL, Rosenwasser LS, Buchmeier AD, Nelson HS. Local nasal immunotherapy for cat allergic rhinitis: clinical and immunologic response. (Abstr). *J Allergy Clin Immunol* 1995;95:305.
19. Schumacher MJ, Pain MCF. Intranasal immunotherapy with polymerized grass-pollen allergens. *Allergy* 1981;37:241-8.
20. Nickelsen JA, Goldstein S, Mueller U, Wypych J, Reisman RE, Arbesman CE. Local nasal immunotherapy for ragweed allergic rhinitis. II° Immunological response. *J Allergy Clin Immunol* 1981;68:41-5.
21. Mathews KP, Bayne NK, Banas JM, McLean JA, Bacon J. Controlled studies of intranasal immunotherapy for ragweed pollenosis. *Int Archs Allergy Appl Immunol* 1981;66:218-24.
22. Foucard T, Bennich H, Johansson SGO. Studies on the stability of diluted allergen extracts using the radio-allergosorbent test (RAST). *Clin Allergy* 1973;3:91-6.
23. Norman PS, Marsh DG. Human serum albumin and tween 80 as stabilizers of allergen solutions. *J Allergy Clin Immunol* 1978;62:314-19.
24. Stewart GA, Thompson PJ, Simpson RJ. Protease antigens from house dust mite. *Lancet* 1989;2:154-5.
25. Thomas WR. Mite allergens groups I-VII. A catalogue of enzymes. *Clin Exp Allergy* 1993;23:350-3.

Efficacy and safety of local nasal immunotherapy

26. Horak F. Local immunotherapy. In: Bonifazi F, Antonicelli AL, editors. Allergen immunotherapy. International Forum of Allergology and Clinical & Immunology, Ancona, Italy. Il Lavoro Editoriale, 1991:109-16.
27. Andri L, Senna GE, Betteli C, et al. Local nasal immunotherapy in allergic rhinitis to *Parietaria*. A double blind controlled study. *Allergy* 1992;47:318-23.
28. Andri L, Senna GE, Betteli C, Givanni S, Andri G, Falagiani P. Local nasal immunotherapy for *Dermatophagoides*-induced rhinitis: efficacy of a powder extract. *J Allergy Clin Immunol* 1993;91:987-96.
29. Andri L, Senna GE, Betteli C, Givanni S, Dimitri G, Falagiani P. Local nasal immunotherapy with extract in powder form is effective and safe in grass pollen rhinitis: a double blind study. *J Allergy Clin Immunol* 1996;97:34-41.
30. Ariano R, Panzani RC, Chiappella M, Augeri G, Falagiani P. Local immunotherapy of seasonal allergic rhinitis in children due to *Parietaria officinalis* pollen. A preliminary report. *Pediatr Asthma Allergy Immunol* 1993;27:227-31.
31. D'Amato G, Lobefalo G, Liccardi G, Cazzola M. A double blind, placebo controlled trial of local nasal immunotherapy in allergic rhinitis to *Parietaria* pollen. *Clin Exp Allergy* 1995;25:141-8.
32. Passalacqua G, Albano M, Ruffoni S, et al. Nasal immunotherapy to *Parietaria*: evidence of reduction of local allergic inflammation. *Am J Resp Crit Care Med* 1995;152:461-6.
33. Andri L, Senna GE. Local nasal immunotherapy (Letter). *Allergy* 1995;50:190.
34. Andri L, Senna GE, Betteli C, et al. Local nasal immunotherapy for birch allergic rhinitis with extract in powder form. *Clin Exp Allergy* 1995;25:1092-9.
35. Piazza I, Bizzarro N. Humoral response to subcutaneous, oral, nasal immunotherapy for allergic rhinitis due to *Dermatophagoides pteronyssinus*. *Ann Allergy* 1993;71:461-9.
36. Mistrello G, Rapisarda G, Falagiani P. Detection of IgE-binding activity in serum after intranasal treatment of normal rabbits with *P. judaica* extract. *Allergy* 1991;46:52-8.
37. Sedgwick DJ, Holt PG. Induction of IgE isotype specific tolerance by passive antigenic stimulation of respiratory mucosa. *Immunology* 1983;50:625-30.
38. Bertoni M, Piccinni MP, Brugnolo F, Emmi L, Maggi E, Romagnani S. Early allergic reaction to nasal specific provocation test: effects of local immunotherapy in patients with seasonal rhinitis (Abstr). *Allergy* 1993;48 (suppl):16.