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Introductory remarks

Conceived for the first time in 1913 by Dunbar (1), the therapy of intranasal administration of increasing amounts of allergens to effect hyposensitization had a revival in the years 1979–86. In these years, seven double-blind, placebo-controlled clinical studies were performed with aqueous extracts, in some cases chemically modified (allergoid) by polymerization with glutaraldehyde (for review, see Passalacqua & Canonica [2]). The local nasal immunotherapy showed clinical efficacy in all but one of the studies, in which a low dose of allergen was employed, and the side-effects were absent or rare.

The powder technology

The reports on the side-effects of injective immunotherapy appearing in the second half of the 1980s aroused interest in local nasal immunotherapy, especially by virtue of its safety. To improve the technology of intranasal immunotherapy, we developed a new technique to formulate the allergenic preparation with a new method of administration. It consisted of the incorporation of the allergen into lactose as inert excipient, at a controlled particle size of 45 µm to ensure the impact on the nasal mucosa, avoiding the passage into the lower respiratory airways (Intranasal Immunotherapy Code Allerkin, Lofarma, Milan, Italy). The powder was encapsulated in gelatin and administered by nasal insufflator. The biologic activity of the product was quantified by the nasal specific provocation test in allergic volunteers and standardized by RAST inhibition as opposed to in-house reference preparation (IHR).

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Kinetics

The absorption into the bloodstream of allergens (Par j) administered intranasally has been clearly shown in preliminary experiments in rabbits (3). Further experiments in human volunteers with radiolabeled allergen (Par j 1) have shown appearance in the plasma 15–20 min and peaks 2–3 h after intranasal administration (4). Interestingly, a relevant fraction of the allergen was retained on the nasal mucosa up to 48 h after administration.

Mechanisms of action

The effects of intranasal immunotherapy on the local inflammatory phenomena have been studied in a double-blind, placebo-controlled study in 20 patients allergic to *Parietaria* by Passalacqua et al. (5). The treatment was preseasonal, and specific nasal provocation tests were performed before the treatment (October), after the treatment and before the beginning of the pollen season (March), and after the pollen season (October). The symptom score after nasal challenge showed a significant ($P=0.007$) reduction in the actively treated group compared with the baseline values. The most important adhesion molecule ICAM-1, key to the inflammatory phenomena at target organ level (in this case, the nasal mucosa), has been extensively studied. ICAM-1 expression on nasal epithelial cells after specific challenge was significantly decreased in the actively treated compared with the placebo group ($P=0.025$), both at the end of treatment and after the pollen season ($P=0.01$). Moreover, a significant reduction of the eosinophils ($P=0.02$) and neutrophils ($P=0.01$) in nasal scrapings, after specific challenge, appeared at the end of the study in actively treated but not placebo-treated patients. The results obtained in the present study provided conclusive experimental evidence of the active effect of intranasal immunotherapy on local allergic inflammation. This decrease of inflammatory parameters was recorded after specific allergen challenge, and therefore corroborates the clinical improvement observed during the allergenic exposure.

An important contribution to our knowledge of the immunologic modifications induced by intranasal immunotherapy came from the study of Giannarini & Maggi (6). Three groups of grass-sensitive patients were studied, those undergoing subcutaneous immunotherapy, those undergoing intranasal immunotherapy, and those untreated. The proliferative response of PBMC (peripheral blood

mononuclear cells) to purified major grass allergen (Rye 1) was evaluated before treatment and during the 2-year subsequent pollination period. The proliferative response of allergen-specific, short-term T-cell lines and production of allergen-driven cytokines by PBMC were also assessed. The clinical symptoms in season and the levels of allergen-specific IgE and IgG were also evaluated. Both intranasal and subcutaneous immunotherapy regimens appeared to be able to induce a significant change in the proliferative response of peripheral blood T cells to the major grass allergen. In fact, in untreated patients, a marked increase in proliferative response to the allergen was observed during the two pollen seasons in comparison to the levels found before pollination. By contrast, the allergen-driven proliferative response to the allergen remained unchanged before and after pollination in both patients receiving subcutaneous immunotherapy and those receiving intranasal immunotherapy. These data suggest that intranasal immunotherapy, although unable to induce changes in the production of allergen-specific IgE and IgG antibodies, affects the response of allergen-specific CD4⁺ T cells. This effect has been attributed to the induction of T-cell tolerance, on the basis of the following phenomena: the generation of allergen-specific suppressor T cells, clonal anergy or extrathymic deletion of allergen-reactive T helper cells, and the switch from TH2 to TH1.

An interesting aspect of this comparative study was the observation that the same immunologic effects were achieved with the two immunotherapy regimens although the total dosages were consistently different, the intranasal dosage being 10–50 times less than the subcutaneous dosage. The explanation is that the great majority of allergen-specific T cells accumulate in the lymph nodes draining the upper respiratory mucosa, and therefore the intranasally introduced allergens can modify them more easily than the subcutaneously introduced allergens. By contrast, after subcutaneous administration, a substantial part of the allergen is dispersed in organs and tissues without immunologic activity and probably destroyed.

The clinical studies

This innovative product has undergone nine double-blind, placebo-controlled clinical trials, which represent the great part of the recent literature in the field. Two studies were performed with grass pollens mix, on a total of 56 patients (7, 8), four studies were done with *Parietaria* on a total of 83 patients (5, 9–11), one study was done with

Dermatophagoides pteronyssinus/*D. farinae* on 24 patients (12), and two studies were done with *Betula*/*Alnus* on a total of 52 patients (13, 14). In all the studies, the clinical efficacy of the treatment was demonstrated, and confirmed by statistical analysis. The side-effects were absent in all but two of the studies, in which rare and mild (local) side-effects were recorded (11, 13). The nasal reactivity, measured by allergen-specific nasal provocation test, was decreased in all the studies. In four studies, serum specific IgE was measured, and no significant variations were observed.

In conclusion, the clinical efficacy of intranasal immunotherapy has been widely demonstrated. This efficacy has been fully acknowledged by the WHO 1997 Position Paper, which stated that "intranasal immunotherapy provides evidence that this form of therapy may be a viable alternative to parenteral injection therapy to treat allergic airways diseases" (15).

As regards short-term efficacy, clinical study with perennial (*Dermatophagoides*) and seasonal allergens (grass and *Parietaria*) showed after 6 months of intranasal immunotherapy a significant improvement of clinical signs

of allergic rhinitis (obstruction, rhinorrhea, sneezing, and itching) and reduced drug consumption (16).

As regards long-term efficacy, a 3-year, long-term follow-up of intranasal immunotherapy with *Parietaria* showed that the protective effect of immunotherapy against nasal symptoms and neutrophil infiltration after specific nasal challenge persisted up to 12 months after suspension of immunotherapy (17).

Conclusions

Clinical efficacy, good tolerability, and safety support the use of intranasal immunotherapy as a valid option for the treatment of respiratory allergy. Both immunologic changes and kinetics show that intranasal immunotherapy is not only a local immunotherapy leading to local immunologic modifications, but is also a systemic therapy inducing systemic effects.

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