

Local nasal immunotherapy: experimental evidences and general considerations

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The possibility of local hyposensitization in allergies was envisaged since the first decades of the century and then sporadically employed, whereas controlled clinical trials of local nasal immunotherapy (LNIT) were performed only during the last 20 years. Studies currently available agree on the clinical efficacy of the treatment. LNIT was demonstrated capable of reducing symptoms both in pollen- and mite-induced rhinitis, and of modifying the specific target organ responsivity. Indeed, aqueous extracts appeared to be more effective than modified ones but were also charged by troublesome local side effects, while the recently introduced powdered extracts seemed to overcome this problem, maintaining a favourable clinical effectiveness. In a recent study we demonstrated a significant effect of LNIT on local allergic inflammation. LNIT reduced both the inflammatory infiltration and ICAM-1 expression on nasal epithelial cells upon specific nasal challenge. The effects on specific challenge appeared long-lasting, but the clinical efficacy seemed to depend strictly upon preseasonal treatment. LNIT with powdered extracts appears an effective, safe and well-tolerated treatment for allergic rhinitis. Nevertheless, its particular administration technique requires a careful choice of patients. Finally, a socioeconomical analysis shows a favourable cost/benefit ratio for LNIT if compared to classic subcutaneous immunotherapy.

Key words: local nasal immunotherapy;
powdered extracts; allergic inflammation.

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Allergen-specific immunotherapy (IT) represents an important therapeutic tool for the treatment of respiratory allergic disorders. Traditional subcutaneous IT (SIT) is able to modify the natural history of the disease and to modulate the immune responses, as proved in many experimental trials (1). Nevertheless the safety issue was addressed in the experimental research to the development of alternative routes of administration: the oral (OIT), the sublingual (SLIT) and the local nasal (LNIT) ones appeared to be of promising interest in this sense (2).

The feasibility of the desensitization of nasal mucosa, the target organ of hayfever, through the intranasal administration of the offending allergen has been envisaged since the first years of the century (3). Nevertheless, during subsequent years this observation remained of limited interest and it was only sporadically developed until the 1970s. In

this decade, local nasal immunotherapy (LNIT) aroused new interest as a practical therapeutic option, and several studies (4–8) appeared. The important problem of SIT adverse effects (9) further encouraged the search for safer routes of administration of IT, and new rigorous studies of LNIT were published in subsequent years (10–23). To date, about 20 controlled studies on LNIT are available in the international literature, as shown in Table 1. Furthermore, an additional large number of open studies and preliminary reports about LNIT, herein not considered, is also available.

Experimental results: efficacy, safety, side effects

The published studies agree on the clinical efficacy of LNIT (Table 1): a clinical improvement

Table 1. Nasal immunotherapy double-blind studies

Author (Ref)	Allergen	Type	Pat	Clin eff.	Side eff.	Nasal react	Serum IgE
Johansson et al. (7)	Grass	mod	23	++	rare	—	NA
Schumacher & Pain (8)	Grass	mod	20	+	none	—	NA
Nickelsen et al. (10)	Ragweed	aq/mod	67	++/+	freq/rare	+	—
Welsh et al. (11)	Ragweed	aq	20	+	freq	NA	=
Georgitis et al. (13)	Grass	aq/mod	50	++/+	freq/rare	=	+
Georgitis et al. (13)	Ragweed	mod	30	=	rare	NA	NA
Georgitis et al. (14)	Ragweed	mod	31	++	rare	NA	NA
Gasparini et al. (18)	Dust mite	powd	20	++	none	NA	NA
Andri et al. (16)	Parietaria	powd	24	++	none	—	NA
Ariano et al. (19)	Parietaria	powd	15	++	none	—	=
Andri et al. (15)	Dust mite	powd	24	++	rare	—	=
Pacor et al. (20)	Grass	powd	24	++	none	=	NA
D'Amato et al. (17)	Parietaria	powd	26	++	rare	—	=
Passalacqua et al. (21)	Parietaria	powd	18	++	none	—	=
Andri et al. (23)	Birch	powd	30	+	none	—	NA
Andri et al. (22)	Grass	powd	32	++	none	—	NA

+: improvement/increase; —: worsening/decrease; =: unchanged; NA: not assessed; aq = aqueous; mod = modified; powd = dried powder.

(symptom/medication scores) was constantly observed in the actively treated groups, although depending upon the type of extract used. Actually, treatments employing low doses appeared to be less effective than those with higher dosages (13, 14) and aqueous extracts were observed to be more effective than modified extracts (10, 12, 24). Recently, powdered extracts have been proposed: this type of preparation shows an efficacy comparable to aqueous preparations (15–18, 21–23). Furthermore, dried-powder extracts significantly reduce nasal reactivity and show satisfactory clinical efficacy and absence of side effects (14, 16–18, 22, 23). Finally, the theoretical risk of asthma attacks (due to allergen inhalation) has been envisaged, but this kind of side effect is only an anecdotal report (17).

In some studies (11–13) patients frequently experienced local side effects (sneezing, rhinorrhoea, nasal blockage). They were sometimes so important and troublesome as to make questionable the clinical usefulness of the treatment: symptoms under allergen exposure were reduced, but their presence was also prolonged during the treatment period. The intensity of local side effects is clearly related to the extract employed: aqueous extracts exhibited very satisfactory effectiveness and the highest incidence of side effects, while modified extracts showed few or no side effects, but a less pronounced efficacy. The recent research provided an interesting solution: dried-powder allergenic extract. This formulation allows the calibration of the aerodynamic mass of the particles (40–50 µm), in order to obtain a total mucosal deposition and to avoid possible inhalation of the

extract into the bronchi. Powdered extracts seem to be devoid of local side effects and exhibit a clinical effectiveness comparable to the aqueous ones. Furthermore they are stable, easily standardizable and allow reproducible predosed administration.

Technical characteristics

LNIT treatments are usually administered through a proper nasal insufflator: aqueous extracts are contained as solution in the device, while powdered extracts are usually prepared as predosed capsules to be broken and then inhaled. Insufflations are usually preceded by nasal administration of cromolyn, with the prudential aim of preventing local side effects. Patients also must vocalize during the insufflation in order to avoid allergen inhalation into the respiratory tract.

As with for subcutaneous IT, the treatment consists of a build-up phase with increasing doses assumed daily or three times a week, followed by a maintaining phase, where the maximal dose is assumed once or twice a week. The course of treatment is preseasonal (2–12 weeks) for pollens and continuous (up to 6 months) for mites.

Mechanisms of action: hypotheses

The pivotal hypothesis supporting the rationale of local immunotherapy is the possibility of achieving a local mucosal tolerance. Some convincing experimental evidence from basic immunology studies were provided: in mice, tolerance (decreased IgE production) can be obtained with local antigen

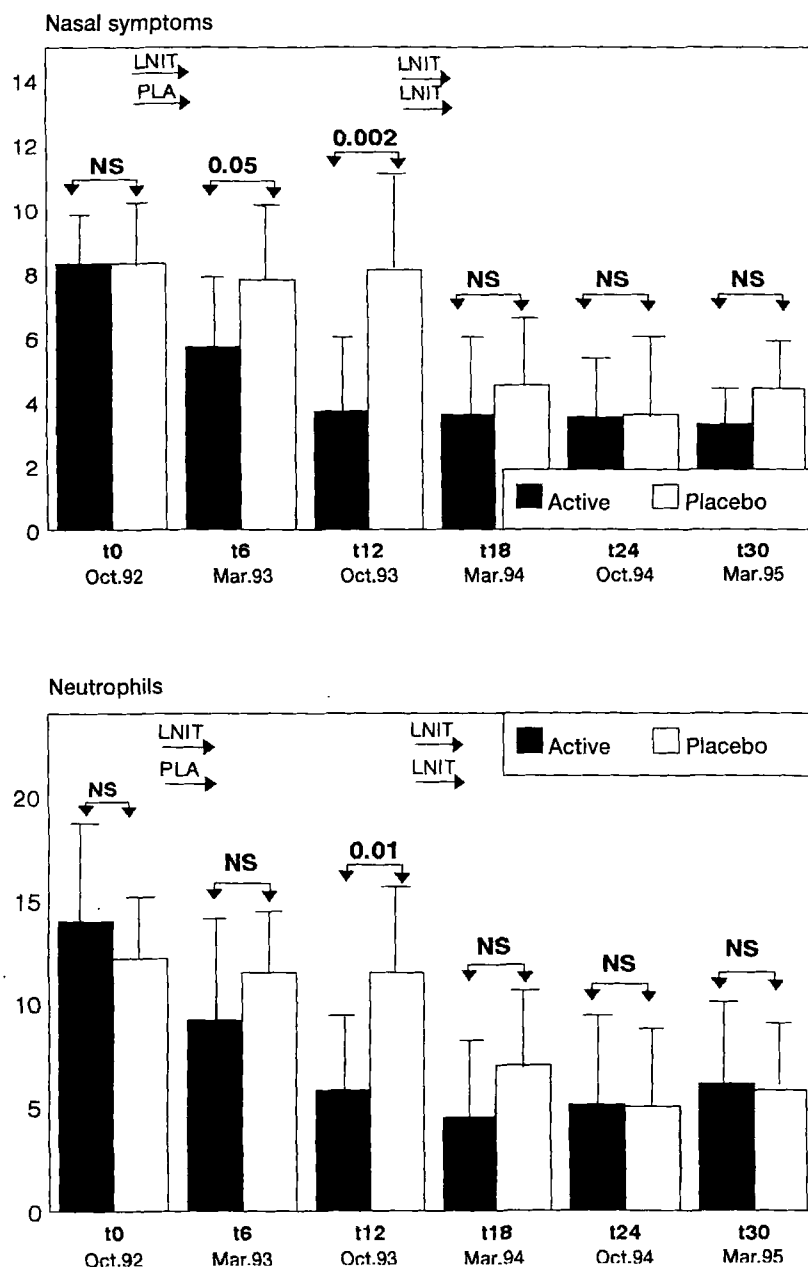


Fig. 1. Symptom+drug intake score (mean, SD) during pollen seasons. The intergroup comparisons are shown in the graph.

administration (25–28), remaining systemic and local immunity dissociated (29). In addition, a possible systemic distribution of inhaled allergens can be hypothesized on the basis of kinetics studies (30).

In humans, both mucosal antibody response and systemic immunological modifications do not correlate with clinical efficacy, as shown by the clinical studies. In this sense, both local and systemic antibodies behaviour after LNIT remains of uncertain significance and does not appear to be involved as the main mechanism of action.

LNIT, local allergic inflammation and kinetic of the allergen: experimental evidence

We investigated the possible actions of LNIT on allergic inflammatory phenomena, using the model of specific nasal provocation test (SNPT). Twenty subjects with single sensitization to parietaria, suffering from rhinitis, were enrolled. The study was conducted in double-blind fashion for the first year (21); subsequently the placebo patients switched to active treatment, and in the third year no patient received LNIT (manuscript in preparation).

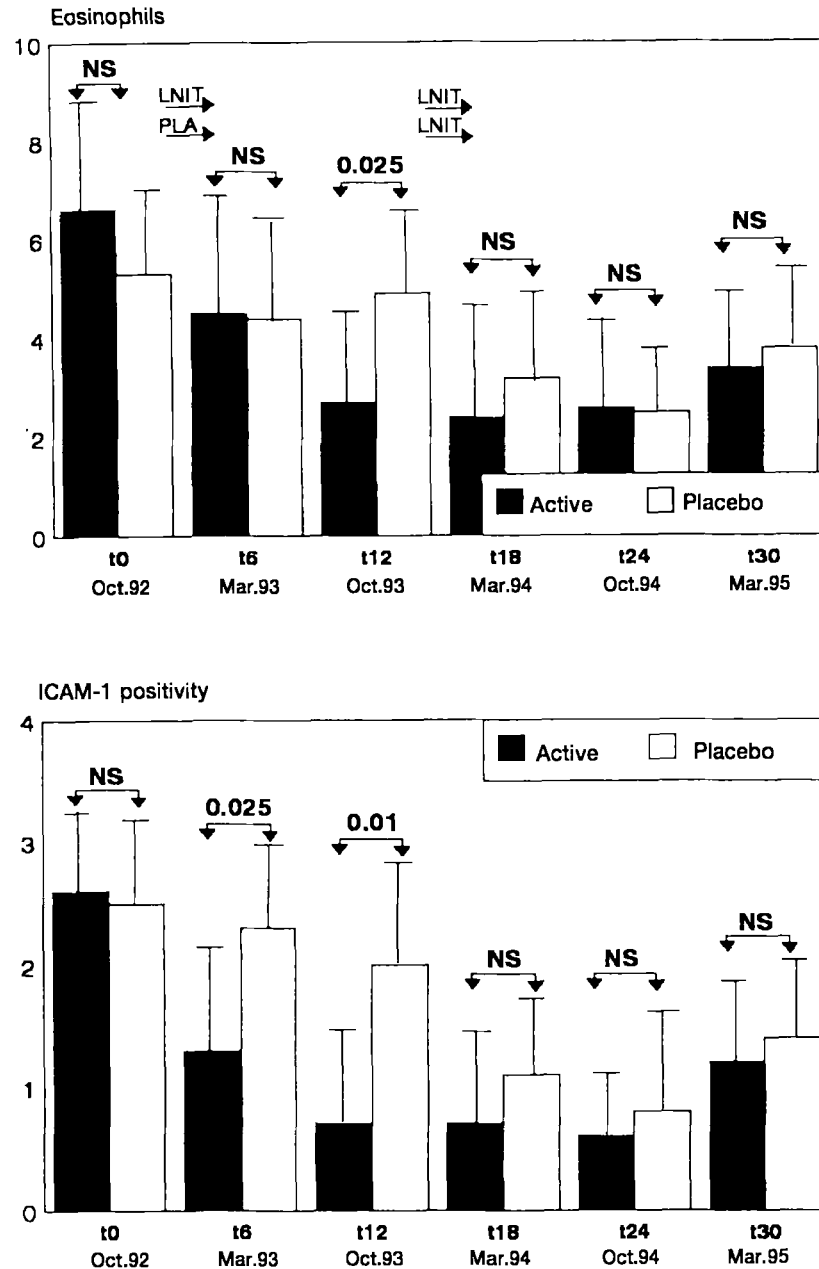


Fig. 2. Upper panel: nasal symptoms, lower panel: neutrophils count. Mean values and SD 30' after specific challenge are shown. The intergroup comparisons are reported in the graph.

The symptoms/medications scores under natural allergenic exposure improved only in the actively treated group after the first year, then a similar improvement was also observed in the former placebo group (Fig. 1). After LNIT suspension clinical relapse was observed in both groups. Interestingly, a significant reduction of symptoms, neutrophilic and eosinophilic infiltration after SNPT in the active treated group in the first year and similar results in the former placebo group in the second year were observed. Identical behaviour was found for ICAM-1 expression on epithelial cells (Figs 2

and 3). The reduction of allergen-induced inflammatory events persists 12 months after the last LNIT course, although both ICAM-1 expression and eosinophils count show an increasing trend at *t*24 and *t*30. These results formally demonstrate the capacity of LNIT in modulating the local inflammatory phenomena due to allergic reactions, both at cellular and molecular level.

We recently performed preliminary experiments on the kinetic (absorption and fate) of the allergen administered by noninjective routes. Briefly, 50 micrograms of ^{125}I -labelled Par J I (about 3.5 mCi)

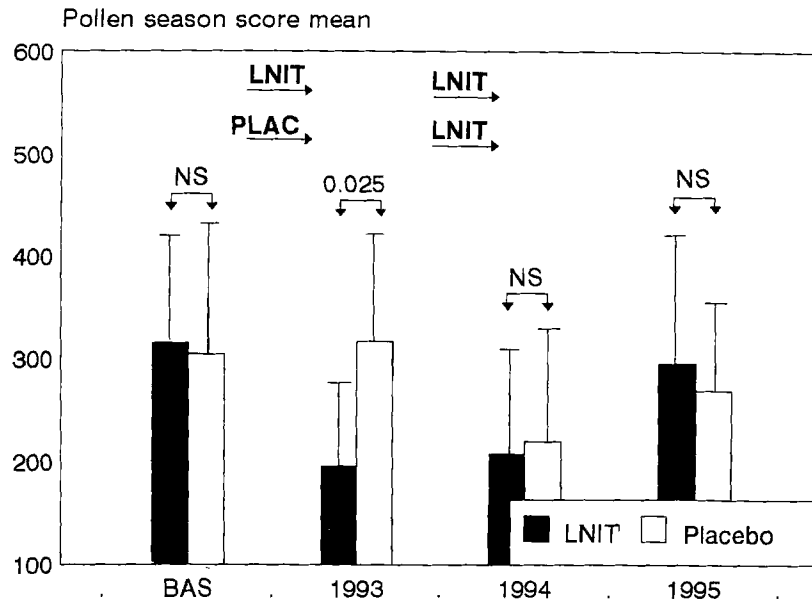


Fig. 3. Upper panel: eosinophils count, lower panel: ICAM-1 positivity on epithelial cells. Mean values and SD 30' after the specific challenge are shown. The intergroup comparisons are reported within the graph.

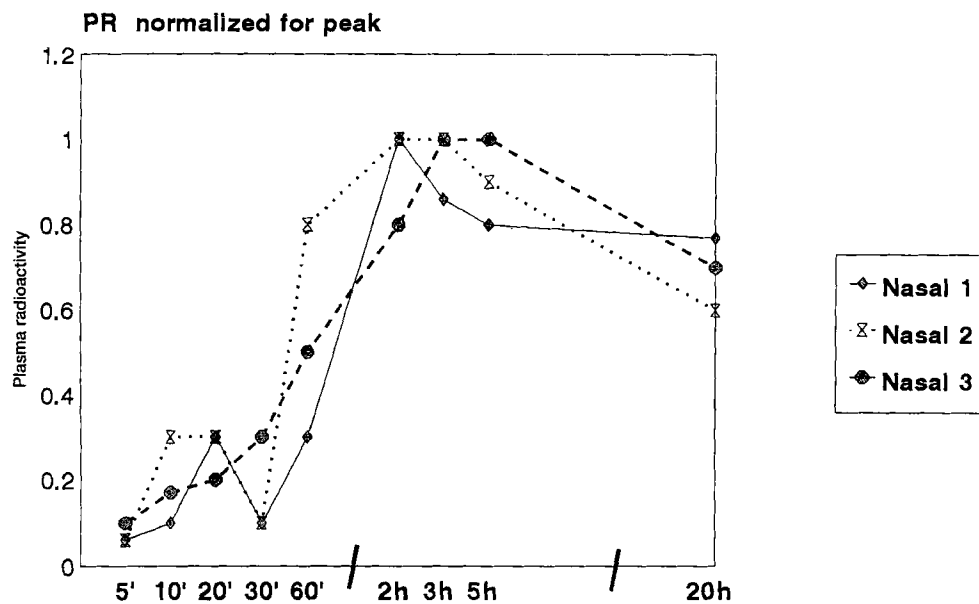


Fig. 4. Plasma radioactivity (normalized for peak) at different times after intranasal ^{123}I ParJI administration in three healthy subjects.

were administered intranasally to three healthy subjects; early dynamic and late static scintiscans were then acquired and blood samples were collected for total plasma radioactivity evaluation. We found that a relevant amount of the allergen was taken to pharynx and oesophagus by mucociliar clearance and plasma radioactivity began to increase after this passive swallowing (Fig. 4). Moreover, a significant amount of the allergen persisted on nasal mucosa up to 48 h after administration. The kinetic of ^{123}I Par J I significantly

differed from that of free iodine administered to one volunteer of the same group. Interestingly, no allergen was detected in the bronchial tree after insufflation.

Concluding remarks

LNIT appears to be a clinically effective treatment for allergic rhinitis due to pollens and dust mites. The suspicion of clinical unusefulness (31) of this route is in contrast with experimental evidence, and

does not take into consideration the recent introduction of powdered extracts (32). In addition, LNIT is usually well accepted and well tolerated by the patients mainly because of self-administration. Nevertheless, LNIT requires a peculiar administration technique (premedication with cromolyn and vocalization during insufflation). Thus, patients eligible for this treatment are to be carefully selected, as reported in Table 2.

Finally, the economical aspect of LNIT is not negligible, as shown in Table 3: particular attention must be paid to the "social cost" of SIT in terms of loss of working time. From this viewpoint, LNIT allows a significant social saving that should be added to the favourable risk/benefit ratio.

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Table 2. Patients eligible for local nasal immunotherapy

- Rhinitis patients
- Adult patients
- Well trained/coordinated patients
- Previous severe reactions to subcutaneous IT
- Refusal of subcutaneous IT
- Low compliance to subcutaneous IT due to lifestyle/working habits

Table 3. Immunotherapy costs per year (approx. data from Italian market)

	LNIT		SIT	
Patient's costs	300	\$	200	Treatment
	—	\$	200	12 injections per year
	300	\$	200	Allergist's controls
	3 visits		2 visits	
Social cost	—	\$	480	Loss of working time per 12 injections
Total	600	\$	1080	Total

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