

Nasal immunotherapy in pollen-sensitive children

Cserhádi E, Mezei G. Nasal immunotherapy in pollen-sensitive children.
Allergy 1997; 52(suppl 33): 40-44. © Munksgaard 1997.

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Subcutaneous specific immunotherapy has a considerable risk of side effects, including severe life-threatening ones or even death. The disadvantages and problems of this kind of therapy gave rise to looking for new ways of hyposensitization. In allergic rhinitis the local (nasal) immunotherapy may be effective. We studied the efficacy of local nasal immunotherapy (Allerkin^R) in grass and ragweed allergic children suffering from seasonal atopic rhinitis. Patients: 36 children (12 with grass pollen, 12 with ragweed pollen immunotherapy, 12 controls). Methods: nasal provocation tests with increasing doses of Allerkin, skin prick test, diary cards. Schedule of the investigations: enrollment of the patients and nasal provocation tests; grass pollen and ragweed pollen preseasonal immunotherapy with increasing doses of Allerkin; during pollen season registration of symptoms and drug consumption; after the season nasal provocation tests. Results: grass immunotherapy: nasal provocation threshold increased ($P < 0.01$), symptoms became fewer ($P < 0.01$) and drug consumption was less in the active group compared to control. Similar but less expressed tendencies were seen in the ragweed group. After the second year of immunotherapy the need for steroid treatment was significantly ($P < 0.05$) fewer in the immunotherapy group than in the control group. No side effects appeared during the course of immunotherapy, but some patients suffered from mild sneezing or nasal discharge after the Allerkin application. Conclusion: local (nasal) immunotherapy is an effective, safe and not troublesome alternative to systemic immunotherapy.

Key words: allergic rhinitis in children; nasal immunotherapy; grass and ragweed sensitivity.

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Accepted for publication 0 Month, 1997

It is well known that parenteral immunotherapy (hyposensitization) in atopic diseases can provoke local side effects and also severe systemic reactions. This is why nonparenteral administration routes of allergenic extracts have been studied. One of the most promising nonparenteral ways of administration appears to be the intranasal application of allergens in allergic rhinitis (1).

The first studies showed that the aqueous and allergoid extracts were clinically effective both for grass and ragweed pollenosis. The results with low- and high-dose local nasal immunotherapy suggested that it was a safe, simple and effective form of immunotherapy when the doses were high enough (2-5).

In 1985 a new powder formulation of allergenic products became available for local nasal immunotherapy. Availability of these new products stimulated a rich series of clinical studies, most of which were double-blind placebo-controlled (6, 7). To

avoid local side effects following allergen administration (e.g. sneezing, itching, rhinorrhoea), disodium cromoglycate was administered as a mast cell stabilizer some minutes before the insufflation of the allergen. The results of these studies have been encouraging with regard to both safety and clinical efficacy in patients allergic to grass pollen, *Parietaria* pollen and house dust mite.

The aim of our study was to investigate the tolerability and efficacy of a pulverized allergen immunotherapy administered nasally to pollen-sensitive children suffering from seasonal allergic rhinitis. We used the following preparations: Allerkin Grass and Allerkin Ragweed, made by Lofarma, Italy. In the course of the study the following parameters were determined:

- nasal sensitivity change upon specific allergen challenge;
- change of the clinical signs (symptom scores during the pollen season);

- change of need for symptomatic drugs;
- safety and side effects of therapy.

The study was an open clinical trial: one group of the patients received intranasal immunotherapy, and the usual symptomatic treatment (antihistamines, etc.); the members of the other group randomized as controls were given only symptomatic treatment without immunotherapy.

Patients and methods

Patients

The patients and their legal representatives (parents) were informed about the purpose of the study, the safety of the therapy, the possible side effects and the duration of the treatment. They signed the information sheet and agreed to participate in the trial. Altogether 36 children were involved in the trial; their basic data are the following:

- 12 children (six boys, six girls), mean age: 13.2 years with grass pollen immunotherapy;
- 12 children (10 boys, two girls), mean age: 12.5 years with ragweed pollen immunotherapy;
- 12 children (nine boys, three girls), mean age: 11.8 years, no immunotherapy.

The inclusion criteria were the following:

- allergic rhinitis (and conjunctivitis) as leading diagnosis;
- seasonal allergic symptoms in the last 2 years;
- severity of symptoms in the previous season; in a score-system with a maximum of 12 points (3–3 given for nasal discharge, sneezing, nasal itching and nasal stuffiness), at least 6 points were reached;
- the patients were dominantly monosensitive to one pollen-group;
- positive skin tests to grass or ragweed pollen (based on a prick test with a Lofarma product);
- positive nasal provocation test performed with specific (grass or ragweed) allergen (Allerkin test, Lofarma), and after the nasal challenge the children were randomized (into immunotherapy group or control group);
- age 4–18 years.

Exclusion criteria were the following:

- severe skin alteration, severe atopic dermatitis on the extremities which make skin testing impossible;
- bronchial asthma;
- other nasal diseases: nasal polyp, severe septum deviation, etc.;
- previous immunotherapy;
- severe systemic disease;
- perennial nasal allergic symptoms which make the nasal provocation impossible.

Methods

Skin prick tests with Allerkin Grass and Ragweed (together with histamine and negative control tests) were performed, using nasal provocation tests with increasing doses of allergen (Allerkin Grass or Ragweed) until clinical signs (sneezing, nasal discharge) appeared. The concentration of allergen causing nasal discharge was estimated as the nasal provocation threshold of the patient.

Patients' diaries contained the nasal (obstruction, itching, discharge and sneezing), conjunctival (runny eyes, redness and itching), tracheobronchial (coughing) complaints and the symptomatic anti-allergic drug consumption/day.

The characteristics of Allerkin Grass and Ragweed used in the trial are as follows:

- the allergen is in the form of macronized powder;
- the antigen is incorporated with 25 mg of lactose;
- the size of the corpuscles is 35–45 µm in diameter;
- the powder is in a capsule and is introduced by an insufflator into the nose.

In Allerkin Grass therapy pollen extracts of *Phleum pratense*, *Dactylis glomerata*, *Lolium italicum*, *Poa pratensis* and *Festuca elatior* were included. In Allerkin Ragweed the pollen extracts of *Ambrosia artemisiaefolia* and *Ambrosia trifida* were used. There were six capsules of each concentration of allergen: 2.5, 5, 10, 20, 40, 60, 80, 120, 160, 240 allergy units (AU)/capsule.

Study design

- Skin prick test and nasal provocation test at the beginning.
- Preseasonal immunotherapy: Allerkin Grass or Allerkin Ragweed in increasing doses beginning with 2.5 AU and finishing with the highest tolerated dose. The same dose is given every second day, 4–6 times altogether. The patients had the possibility of using disodium cromoglycate before the application of Allerkin.
- In the pollen season, the diary contains the complaints and the specification and dosage of administered symptomatic drugs.
- Postseasonal nasal provocation test.

The control patients were given all the symptomatic drugs they needed but no Allerkin was given to them.

Results

Patients with grass pollen sensitivity

Nasal provocation tests: the tolerance of the nasal mucosa significantly increased in the group treated with Allerkin while there was no change in the control group (Fig. 1). The symptom scores in the

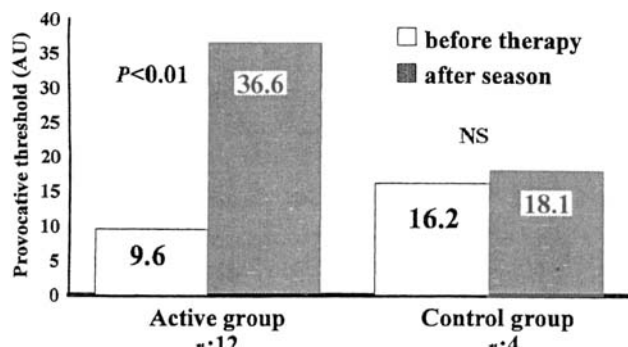


Fig. 1. Nasal provocation test (Allerkin grass therapy).

grass pollen season were significantly lower in the Allerkin group compared to the control group (Fig. 2). Drug consumption was significantly less ($P<0.05$) in May in the actively treated group compared to the control group. In June and July there were no significant differences between the two groups of patients although the members of the actively treated group needed 20–50% less symptomatic drugs than the patients in the control group.

Patients with ragweed pollen sensitivity

Nasal provocation tests: the tolerance of the nasal mucosa significantly increased in the group with Allerkin while there was no change in the control group (Fig. 3). The symptom scores in the ragweed pollen season were lower in the group with Allerkin compared to the control group, but the differences were not significant (Fig. 4). Drug consumption during the ragweed season was only slightly (3–30%) less in the active group compared to the control group.

During the course of immunotherapy some patients suffered from sneezing or nasal discharge after the Allerkin application. The symptoms were mild; none of the patients had to stop the immunotherapy because of these complaints. No side

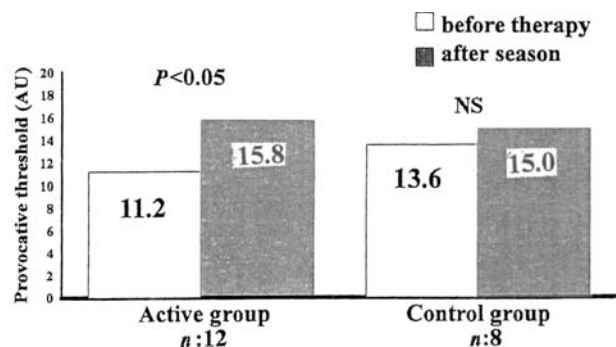


Fig. 3. Nasal provocation test (Allerkin ragweed therapy).

effects appeared during the course of immunotherapy.

This trial was performed in 1993. In the following year (1994) we made observations on the same patients (34 of the 36 participated) after 2 years of immunotherapy. The need for local steroids and the increased use of symptomatic drugs/drug combinations during the pollen season were significantly fewer in the Allerkin group compared to the patients without immunotherapy (Table 1).

Discussion

Specific immunotherapy was introduced in 1911 by Noon and for many years it remained based on empiricism. Standardized and purified extracts increased the efficacy of this therapeutic modality.

This is the only treatment intervention that may alter the natural course of allergic diseases; however, it has been suggested that the long-term anti-inflammatory (e.g. inhaled steroid) treatment may also do the same (8). This kind of therapy is now well accepted as an effective treatment for allergic rhinitis and hyposensitization to venomous stings. Most specialists agree that subcutaneous specific immunotherapy performed with standardized extracts has a good efficacy documented by double-blind placebo-controlled clinical trials.

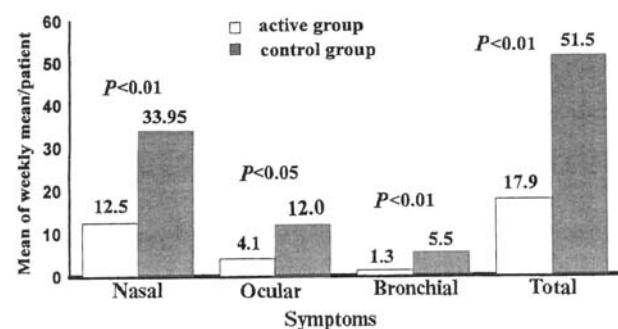


Fig. 2. Symptoms in grass season 1993.

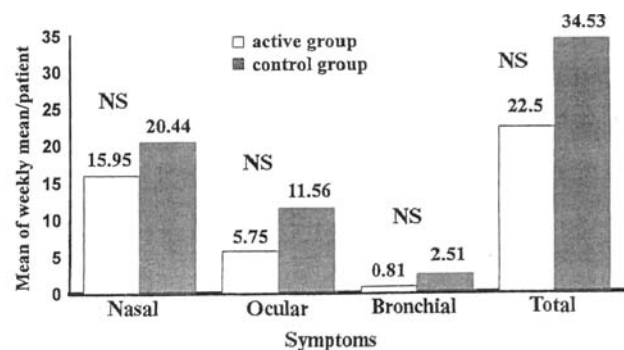


Fig. 4. Symptoms in ragweed season 1993.

Table 1. Clinical observations in seasonal allergic rhinitis with and without Allergen immunotherapy (n: 34) 1994

	Immunotherapy + symptomatic drugs	Symptomatic drugs	
Number of patients	24	10	
Need for local steroids	5 (21%)	7 (70%)	$P < 0.05$
Increase of drug consumption or need for drug combinations	3 (13%)	5 (50%)	$P < 0.05$

It should not be forgotten that this type of therapy involves the risk of side effects, including severe life-threatening ones or even death. Specific immunotherapy must be prescribed and performed by specialists who have clinical practice with this type of therapy and can perform the emergency techniques if needed (9). These disadvantages and problems of subcutaneous immunotherapy have given rise to looking for new ways of hyposensitization.

Recent studies have shown that nasal (6, 7), oral and sublingual (10–13) immunotherapy may be effective. One of the possibilities is to perform nasal specific immunotherapy in patients suffering from allergic rhinitis. D'Amato et al. (7) experienced good results with nasal immunotherapy in patients allergic to *Parietaria* pollen and suffering from hayfever. In other studies the results were less convincing (3, 4). It seems that a local form of specific immunotherapy is indicated in milder nasal allergies, where the symptoms and the need for drugs may be reduced by it. During nasal specific immunotherapy serious systemic or focal reactions are rare. Anaphylactic types of adverse effects will not appear in the course of this therapy. Some patients complain of signs of rhinitis after the nasal insufflation but this can be easily controlled.

This kind of therapy may be performed at home, so the fear of injections and time-consuming visits to the doctor's office will not occur. Compliance with this kind of therapy was very good in most of the trials and our experience has been the same. Our own results with nasal immunotherapy resulted in good clinical effects. Comparing our experiences with grass and ragweed immunotherapy we concluded that the former is more effective than the latter. We have the following possible theories for these differences:

- Ragweed Allergen contains, besides *Ambrosia artemisiaefolia*, also *Ambrosia trifida*; this weed does not exist in Hungary.

- The ragweed allergen is a more aggressive antigen than the grass allergen according to the Hungarian experiences.
- The ragweed sensitive patients also often have some grass sensitivity, and the mild early summer complaints of these patients cause some problems in the course of hyposensitization.

On the basis of our experiences we can conclude that:

- 1) Nasal immunotherapy is safe and well tolerated by the patients and it puts less burden on them than does conventional parenteral immunotherapy.
- 2) The tolerance of nasal mucosa against the specific allergen has significantly increased after nasal immunotherapy.
- 3) During the grass pollen season the treated patients had significantly fewer complaints than the controls; during the ragweed pollen season the treated patients had fewer complaints than the controls, but this difference was not significant.
- 4) The symptomatic drug consumption was less in the treated patients (grass and ragweed sensitive children) compared to the controls, but this difference was only significant in May.
- 5) According to our observations the need for local steroids and the use of symptomatic drugs during the pollen season were significantly fewer in the Allergen group compared to the patients without immunotherapy.

Finally, in conclusion, local (nasal) immunotherapy is a useful alternative treatment possibility in seasonal allergic rhinitis.

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