

Clinical efficacy and tolerability of a steady dosage schedule of local nasal immunotherapy. Results of preseasonal treatment in grass pollen rhinitis

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Background: Local nasal immunotherapy (LNIT) is an effective and safe alternative to conventional subcutaneous immunotherapy. A specific nasal provocation test (SNPT) could be used to indicate the optimal subclinical dose to carry out LNIT.

Objective: We hypothesize that LNIT could be carried out with only one predefined dose for all patients, so we have evaluated the efficacy and the tolerability of LNIT administered at steady dosages in patients with seasonal allergic rhinitis.

Methods: Twenty grass pollen-sensitized patients suffering from seasonal allergic rhinitis were studied in a randomized, double-blind, placebo-controlled trial. The treatment was carried out according to a schedule based on the administration of a steady subclinical dosage of the allergenic extract, selected on the basis of the sensitivity threshold of the SNPT. The patients were divided into two groups of 10 people each, which were treated either with grass pollen extract in a hydroglyceric solution or with placebo.

Results: During the peak pollen period, with regard to the placebo (P) group, in the grass treated (GT) group a significant decrease of both nasal symptoms ($P = .021$) and consumption of antihistamines ($P = 0.047$) was found. Furthermore, only in the GT group was the provocative dose assessed by the SNPT significantly lower ($P = .049$) at the end of the treatment. In this group of patients an inverse correlation between such provocative dose and the nasal symptom score reported during the peak pollen period was also evidenced ($r = 0.708$; $P = .038$). Adverse reactions to LNIT were mild, rare, and did not interfere with the completion of the therapeutic schedule.

Conclusions: Our study indicates that LNIT, when administered at steady dosages, may be proposed as a treatment for grass pollen seasonal allergic rhinitis as it appears to be effective and well tolerated.

Ann Allergy Asthma Immunol 1999;82:47–51.

INTRODUCTION

Over the last 20 years a series of controlled studies has supported the clinical efficacy of LNIT in the treatment of allergic rhinitis, whether seasonal or perennial.¹ Such studies were originally characterized by the use of aqueous allergenic extracts while, later on, they employed modified or powder extracts in order to avoid side effects.^{2–10} The tolerability of powder extracts was

found to be similar to that of placebo although, after the administration of high allergenic doses, some nasal complaints⁶ and very rare attacks of asthma⁷ were reported.

Clinical studies with LNIT so far published have been characterized by the use of a treatment schedule based on the self-managed administration of progressively increasing allergenic doses. Since the dosages are usually higher than the maximum tolerated dose, they may cause a real nasal challenge and give rise to such side effects as, for example, symptoms of rhinitis.

In this placebo-controlled double-blind study we wanted to assess whether LNIT at steady dosage was

capable of effectively controlling the clinical manifestations of seasonal allergic rhinitis in a group of patients sensitized to grass pollens. In this regard, we used a LNIT in a hydroglyceric solution which assures the stability of the allergenic extract.

MATERIALS AND METHODS

Patients

Twenty patients (7 females and 13 males), aged between 18 and 43 years, suffering from allergic rhinitis for at least 2 years were selected (Table 1). The following criteria for inclusion were adopted: (1) typical anamnesis for seasonal allergic rhinitis; (2) marked positivity of the prick tests (3+ or 4+) to an extract of 5 grass pollens in a hydroglyceric solution titrated at 20,000 biologic units (BU)/mL (SARM Allergeni, Guidonia, Rome, Italy), and assessed according to the already known guidelines¹¹; (3) RAST positivity to grass pollens of at least class 2 (Pharmacia CAP system—FEIA); (4) positivity of the SNPT with grass pollens; and (5) written and informed consent. Patients were excluded because of (1) coexistence of recurrent rhinitis and/or nasal polyposis and/or bronchial asthma; (2) sensitization to other allergens; (3) previous specific immunotherapy; (4) chronic use of nasal decongestants or corticosteroids; and (5) pregnancy or lactation.

Allergen

The active product consisted of the same hydroglyceric extract of grass pollen allergens, titrated in BU/mL and used for the prick test (SARM Allergeni, Guidonia, Rome, Italy). This extract delivered a constant and controlled volume of 100 μ L of product at

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Received for publication January 23, 1998.

Accepted for publication in revised form August 20, 1998.

Table 1. General Characteristics of Study Population

	Grass	Placebo	
Mean age (yr)-(±SD)	27.3 ± 7.9	30.8 ± 9.8	NS*
Sex (M/F)	7/3	6/4	—
Years of disease (±SD)	11.6 ± 9.7	12.3 ± 7.5	NS
Pre-seasonal grass-specific IgE	45.6 ± 35	39.3 ± 39.8	NS
Preseasonal SNPT	120.2 ± 42.2	140 ± 51.6	NS

* NS = not significant.

each squeeze. Ninety-five per cent of the nebulized product is composed of particles with a diameter >11.1 µm, a size unable to reach the lower airways, as has been shown by a distribution study with ⁹⁹Tc-DTPA.¹² The placebo consisted of a hydroglyceric solution and was identical in appearance to the active product.

Immunotherapy Program

The LNIT was carried out during the period from January 1 to March 31, 1996 according to a schedule based on the self-administration every second day alternating nostrils each time for a total number of ±40 administrations. The group of patients treated with the allergenic extract received a steady dosage of 50 BU. Such dosage was chosen on the basis of the clinical evaluation of the SNPT carried out at the time of enrollment and was found to be the highest dose tolerated by all the patients.

Experimental Design

Patients were randomly divided into two groups according to the randomization tables.¹³ The treated group (10 patients) received grass pollen extracts, while the control group received the placebo. During the study, both the SNPT and the serum levels of eosinophil cationic protein (ECP) were assessed (Fig 1). The nasal sensitivity was evaluated by the SNPT with grass pollen extract in a hydroglyceric solution, before the start and immediately after the end of the LNIT, during a period when grass pollens were virtually absent. In this regard, increasing doses (12.5; 25; 50; 100; and 200 BU) were administered at intervals of 20 minutes. The provocative dose of allergen was identified from the amount required (1) to increase the total nasal

resistance to airflow of 100% or more as compared with control with a hydroglyceric solution, using anterior rhinomanometry (Rhinospir 164, Markos, Monza, Italy)¹⁴ and (2) to elicit at least two of the following nasal symptoms: itching, sneezing, discharge, and obstruction.¹⁵ The ECP serum levels were determined before the start of LNIT and at the peak of grass pollination (30 May 1996). The analysis of sera was carried out by means of the Pharmacia CAP System—FEIA (Kabi Pharmacia, Uppsala, Sweden), according to the manufacturer's instructions, and expressed in mg/L.

Pollen Count

The pollen count was made during the period from April 1 to June 30, 1996 by a Lanzoni volumetric spore trap (VPPS 2000, Lanzoni, Bologna, Italy). The peak pollen period, arbitrarily defined as the interval during which grass pollen counts exceeded 20 grains/m³, lasted 49 days, from May 5 to June 23.

Clinical Assessment

Clinical assessment was performed at the start and at the end of the treatment as well as at the end of the pollen season. All patients were seen monthly during the treatment period in order to assess their compliance. Further, they kept a daily report of allergic symptoms during both the treatment period and the pollen season. The degree of severity of such nasal symptoms as itching, sneezing, discharge, and obstruction, as well as of such ocular symptoms as itching and hyperlacrimation was recorded on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The patients were instructed both to use antihistamines (loratadine 10 mg, tablets) when needed and to record their amount as well. In order to calculate the consumption of loratadine, 6 points were arbitrarily allocated for each tablet taken per day.

Statistical Analysis

This was performed with software.¹³ Data concerning patients who did not complete all the predetermined evaluations were excluded from the statistical analysis of all designed comparisons except the one concerning the characteristics of the study population admitted to the trial. Differences between the two groups, concerning the above mentioned characteristics,

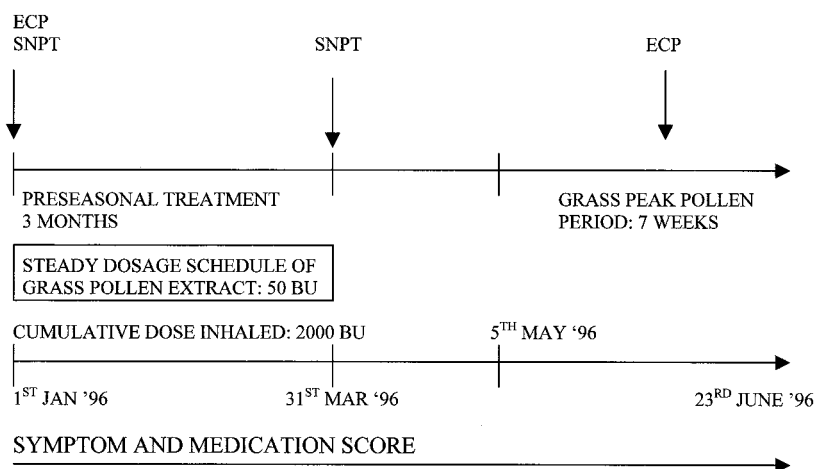


Figure 1. Study design.

the symptom and medication score, the provocative dose of the SNPT, and the ECP serum levels were calculated by Mann-Whitney's U test. Differences within the same group were analyzed by Wilcoxon's test. Spearman's rank correlation test was used for the regression analysis.

RESULTS

As Table 1 shows, taking into account all the inclusion criteria of the trial, both groups of patients were well matched at baseline. Two patients, one for each group, withdrew from the study because of logistic problems. The data expressed in the following text concern the comparison between two groups of 9 patients each. No systemic adverse reactions were reported during the treatment. Mild local reactions characterized by sneezing and discharge occurred in three patients in the GT group during the first 30 minutes after administration; however, this did not interfere with the completion of the treatment schedule.

The cumulative LNIT dose administered in this study was therefore

2,000 BU, approximately 8.5- μ g group 5 allergens, which is more or less the same amount usually employed in an equivalent course of subcutaneous immunotherapy (1,600 to 2,400 BU).

Figures 2 and 3 show the mean weekly symptom medication score (SMS) and drug score for each group during the peak pollen period. With regard to the P group, the GT one had significantly lower SMS ($P = .047$), nasal symptoms score ($P = .01$), as well as solely medication score ($P = .047$). On the other hand, no significant difference was evidenced with regard to ocular symptoms (Table 2).

During the treatment period, the SMS was slightly higher in the GT group than in the placebo one, although not significantly.

With reference to the provocative dose of the SNPT, at the end of the treatment it was significantly higher in the GT group ($P = .049$) than in the P one. Further, no significant differences were noted either within the P group, or in the comparison between the two groups (Table 3). Notably, in the GT

group the regression analysis showed a statistically significant inverse linear correlation ($r = 0.708$; $P = .038$) between the provocative dose of the SNPT performed at the end of the treatment and the mean daily nasal symptom score reported during the peak pollen period (Fig 4).

As far as the ECP assay is concerned, before the start of LNIT, the mean $\pm$ SD values expressed in μ g/L were 4.23 ± 2.46 in the GT group and 6 ± 3.83 in the P group while during the peak pollen period, they were 6.99 ± 4.25 in the former and 7.47 ± 4.79 in the latter. No statistically significant variation was evidenced either within each group or in the comparison between the two groups.

DISCUSSION

It has long been recognized that LNIT is capable of controlling the symptoms of seasonal allergic rhinitis in a dose-dependent manner.^{16,17} At higher dosages, LNIT can sometimes cause local adverse reactions.¹⁸⁻²¹ On the other hand, the studies characterized by a low-dose administration schedule did

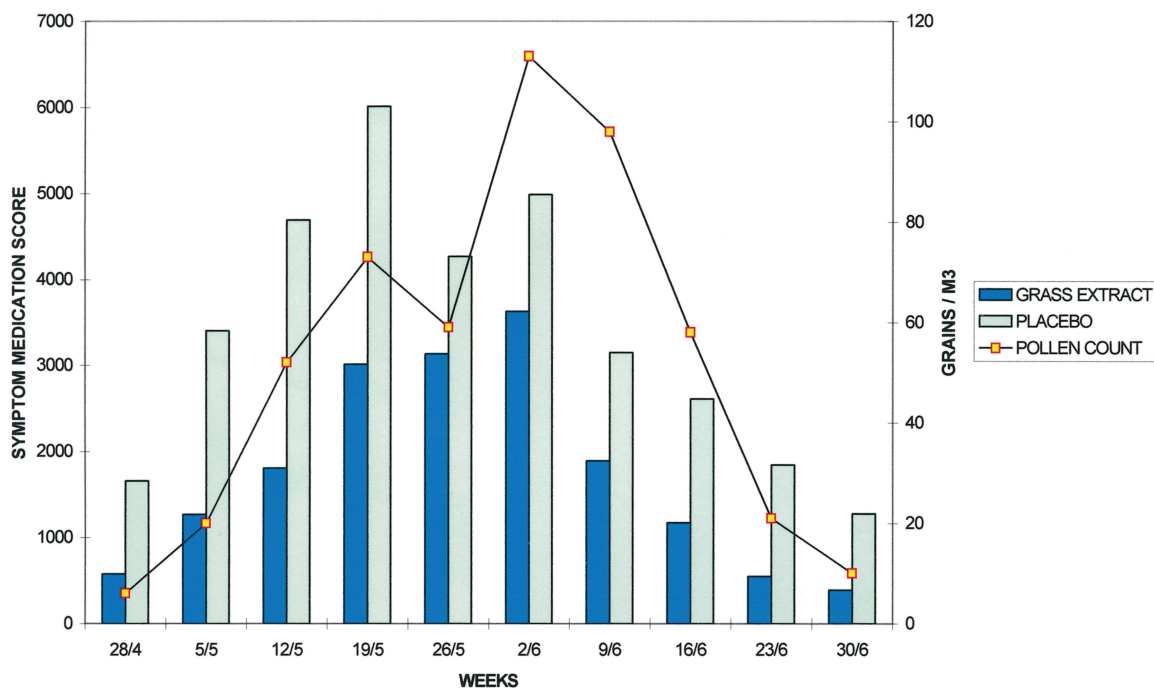


Figure 2. Mean weekly overall symptom-medication score during the peak pollen period.

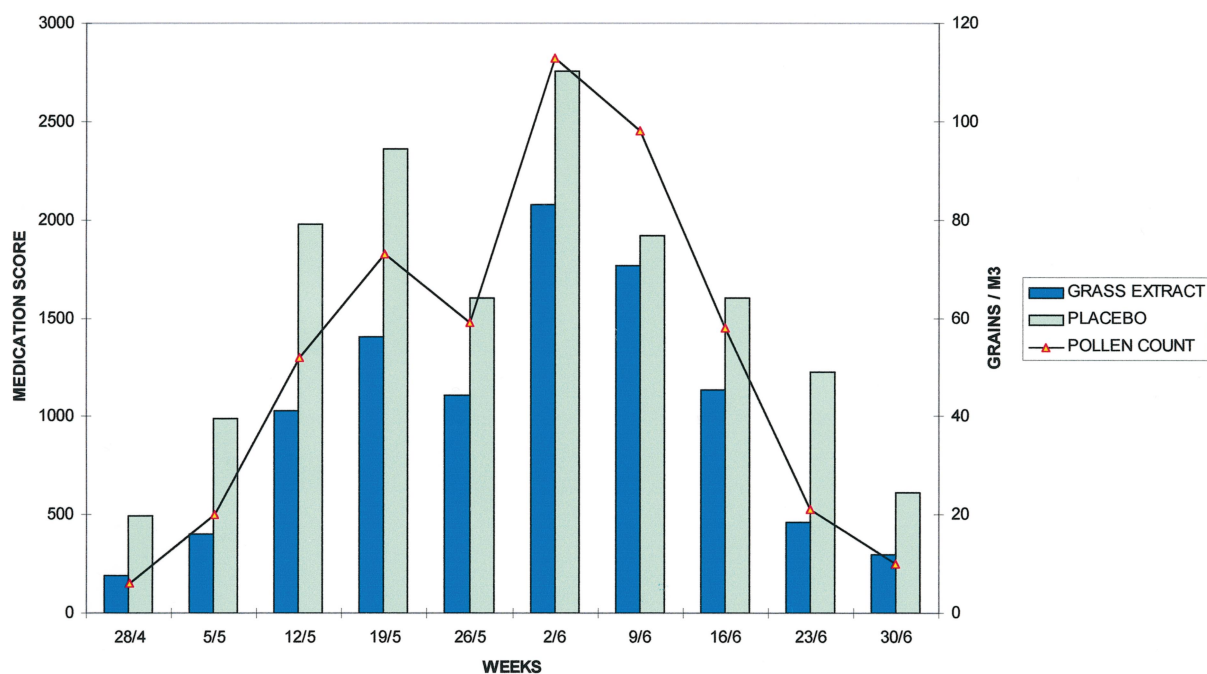


Figure 3. Mean weekly medication score during the peak pollen period.

not show a clinical effectiveness although tolerance was found to be good.^{17,22} In our study, LNIT with hydroglyceric extract of grass pollens administered by a steady dosage schedule, was found to be clinically effective and well tolerated. Nasal symptoms and consumption of antihistamines were found to be significantly lower in the GT group as compared with the control one. Furthermore, only in the former was the nasal sensitivity to grass pollens significantly reduced at the end of the treatment. In this group of patients, an inverse correlation between the provocative dose of the SNPT carried out at the end of the treatment and the nasal symptom score during the peak pollen period was also demonstrated. To our knowledge no similar observation has so far emerged in international literature. As the results show, ocular symptoms also decrease in the treated patients but the difference was not significant. This seems to indicate only local effects of LNIT although further studies are necessary to ascertain whether this is true.

With reference to the results of the ECP assay, contrary to what is stated

Table 2. Mean Weekly Symptom and Medication Score During the Peak Pollen Period

	Treatment		P
	Grass	Placebo	
Nasal symptoms	20.61 ± 15.18	44.94 ± 25.02	.01
Ocular symptoms	5.51 ± 4.75	3.9 ± 4.81	NS*
Medication score	7.28 ± 8.82	23.14 ± 22.63	.047
Overall symptom-medication score	26.12 ± 17.07	48.82 ± 27.02	.047

* NS = not significant.

Table 3. Mean Provocative Dose Assessed During the SNPT

Treatment	Provocative Dose		P
	Pretreatment	Posttreatment	
Grass	122.2 ± 44.1	188.9 ± 105.4	.049
Placebo	144.4 ± 52.7	177.8 ± 139.4	NS*

* NS = not significant.

in the literature,^{6,23,24} this serum marker did not seem useful in monitoring the efficacy of LNIT as, with regard to baseline, no statistically significant variation was found during the peak pollen period either in the P group or in the GT one. As far as the tolerability of the treatment is concerned, it was good because the adverse reactions were

rare and mild and in any case they did not interfere with the completion of the treatment schedule.

In this study, the data concerning the clinical efficacy of LNIT seem to be particularly important as they were obtained with an administration schedule characterised by a relatively short duration (only 3 months) and by a lower

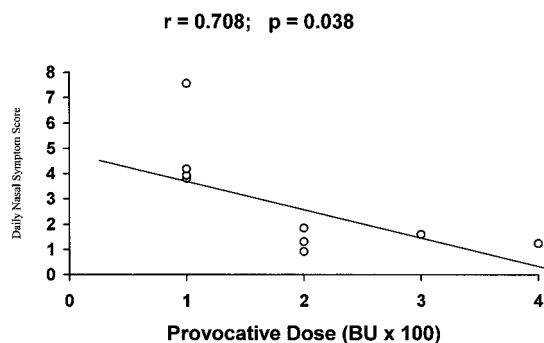


Figure 4. Linear correlation between the provocative dose of the post-treatment SNPT and the daily nasal symptom score during the peak pollen period in the grass treated patients.

cumulative dose than the one which is recommended by the manufacturer (2,000 BU versus 3,790 BU).

In conclusion, the LNIT used by us, administered at steady dosage, may be proposed as a treatment for grass pollen seasonal allergic rhinitis because it appears to be effective and well tolerated. According to recent suggestions,¹ the schedule based on repeated administrations of the same subclinical dose, selected on the basis of the SNPT sensitivity threshold, seems to be a good therapeutic approach for LNIT. The results of our study will need further confirmation by studies performed on larger populations.

ACKNOWLEDGMENTS

Doctor Lucia Livantino of the Unit of Laboratory Medicine of Misericordia e Dolce Hospital, Prato, is gratefully acknowledged for her contribution in the ECP assay.

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