

Local nasal immunotherapy: efficacy and tolerability of two different administration schedules in grass pollen rhinitis

G. E. Senna, G. Andri*, A. R. Dama, P. Falagiani* * and L. Andri

Allergology Service, Ospedale Maggiore. Verona. Italy. * General Medicine. Ospedale di Manerbio, Brescia.

** Scientific Direction. Lofarma SpA. Milan. Italy.

SUMMARY

Background: efficacy and safety of local nasal immunotherapy has been demonstrated by many placebo-controlled clinical trials. The treatment schedule consists of an induction phase at increasing dosages followed by a maintenance phase. Aim of present study has been to evaluate a new simplified treatment schedule at constant dosage.

Methods and results: 26 grass-allergic rhinitic patients have been treated according to the new constant dosage schedule, while 15 patients in a control group were treated with conventional incremental dosage schedule. A commercial preparation of allergens incorporated into powder (Allerkin®). The total cumulative dosage administered with conventional schedule resulted higher than simplified constant schedule (5,025 vs 3,000 AU). To evaluate efficacy, symptom and rescue medication scores were recorded during the spring pollen season, and a subjective overall evaluation was asked to the patients at the end of the season. The analysis of scores showed that the two treatment schedules were equivalent as regards both efficacy and safety, being side effects light and restricted to the administration site (sneezing).

Conclusions: the use of a constant dosage schedules is suggested for the administration of local nasal immunotherapy, having as advantage a better simplicity. Avoidance of mistakes in dosages is considered important in a therapy which is self-administered by patients.

Key words: Allergic rhinitis. Grass allergy. Local nasal immunotherapy. Constant dosage schedule. Incremental dosage schedule.

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INTRODUCTION

Specific immunotherapy (IT) for the treatment of allergic diseases is world-wide accepted as the main etiological therapeutical tool, as demonstrated by many double-blinded placebo-controlled clinical studies, recently reviewed by Abramson in a meta-analysis study (1). The reports on some severe adverse events in the course of injective subcutaneous IT in the second half of the eighties induced many clinical investigators to study new non-injective administration routes, especially for safety reasons: oral, sublingual and local nasal (LNIT) immunotherapy. With the exception of oral IT, where many clinical studies failed in achieving significant clinical results, sublingual and local nasal immunotherapy can be considered clinically effective and safe (reviewed in 2). As regards LNIT, its ability to reduce rhinitic symptoms and medication usage, as well as to decrease nasal reactivity towards offending allergen has been well established (3-24), and on the basis of these studies the WHO Position Paper on allergen immunotherapy accepted as valid this therapeutic option (25). Many of the controlled clinical studies have been performed with allergens in powder form, obtained by incorporating allergens into a powder excipient (lactose) and characterized by a macronized particle size to prevent bronchial inhalation (14-24), having besides the consistent advantage of a prolonged stability (26). Commercial set treatments for LNIT are available, which are usually self-administered by the patients themselves. One of the problems of this kind of therapeutical approach is the complexity of treatment schedules, especially in the first initial treatment phase where many increasing dosages must be administered following a precise calendar. Errors, e.g. self-

Table I
Demographic data of study populations

| | Incremental dosages | Constant dosage |
|-----------------------------|---------------------|-----------------|
| N.° Patients | 15 | 26 |
| Gender (males/females) | 7/8 | 18/8 |
| Mean age (years) and SD | 26.4 ± 9.8 | 29.0 ± 9.4 |
| Duration of disease (years) | 6.3 | 5.8 |

administration of wrong dosages, cannot be excluded, therefore a strict selection of patients is necessary. Aim of present open study is to evaluate the efficacy and safety of a new simplified administration schedule for LNIT in grass pollen rhinitis, consisting in the administration of a constant dosage. The control group was treated according to the conventional schedule at increasing dosages.

MATERIAL AND METHODS

Patients

Forty one consecutive outpatients have been selected (table I). Inclusion criteria have been:

- typical history of grass allergic rhinitis, with a peak of symptoms from the end of April to June;
- positive skin prick test to grass pollen, with a minimum wheal of 5 mm (extracts from Lofarma SpA, Milan, Italy);
- RAST positivity, at least class 3 (Sferikit®, Lofarma SpA, Milan, Italy);
- availability to sign informed written consent.

Exclusion criteria have been: asthma, long term use of nasal steroids or decongestants, prior specific immunotherapy, state of pregnancy or lactation, presence of nasal polyps or other diseases or malformations causing nasal obstruction.

Identification of the nasal threshold

A preliminary study has been performed before the starting of present trial to identify the mean nasal provocative threshold, finalized to establishing the dosage to be adopted in the constant dosage schedule. To this aim 151 grass-allergic outpatients (different from those enrolled in present study) have been submitted to nasal provocation test with grass powder allergens (Allerkin® Test, Lofarma, Milan, Italy) with increasing doses of 2.5, 5, 10, 20, 40, 60, 80 AU at 10-minute intervals and with rhinomanometric

assessment after each challenge (27). The test was considered positive for the allergen dose that caused an increase of resistance of 100% or more (27). The mean provocative dose resulted to be 39.7 AU (SD 26.2 AU). On this basis the 40 AU dosage as been identified as mean threshold dose, sub-provocative in some patients, provocative (with mild symptoms) in other patients.

Immunotherapy treatment

The treatment product (Allerkin®Grass, Lofarma, Milan, Italy) consisted of grass pollen mixture allergens (*Phleum pratense*, *Dactylis glomerata*, *Lolium italicum*, *Poa pratensis*, and *Festuca elatior*, 20% each) incorporated into lactose powder. The particle size of the powder was 45 µm (partition value 50%/50%) as determined by laser-light-powered analysis at wavelength 632.8 nm (analyser Cylas 715, Marcoussis, France). The powder was held into rigid gelatine capsules and was administered by a nasal insufflator (Plastiape, Osnago, Italy). The product was titrated in allergenic units (AU) defined as 1/40 of the mean provocative dose by specific nasal challenge in allergic volunteers (25). The product was standardised in order to assure batch-to-batch consistency by RAST-inhibition procedure in comparison to an in-house reference preparation (26).

The treatment has been performed according the following two schedules:

a) Incremental dosage schedule: increasing dosages from 2.5 AU up to 240 AU were administered on alternate days and alternating nostril, the dosage was reduced to 1/3 (80 AU) during the last 5 weeks, due to the presence of pollen grains in the atmosphere (Fig. 1). For each patient the mean cumulative dose administered was 5,025 AU. Fifteen patients have assigned, according to a randomization list, to this schedule.

b) Constant dosage schedule: 40 AU were administered three times weekly during the whole study (Fig. 1). The mean total dose administered to each subject was 3,000 AU. Twenty-six patients have been assigned to this schedule.

Both the treatments lasted from 15th October to 15th April (table II).

Evaluation of symptoms and medications

During the treatment the patients were instructed to record eventual adverse reaction in a diary card. The evaluation of efficacy has been done during the grass pollen season from 15th April to 15th June (table

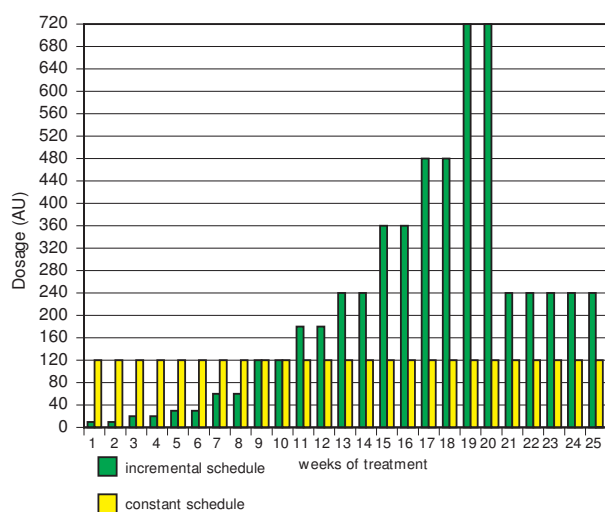


Figure 1.—Cumulative dosage per week with the two schedules under study.

II) with a diary card where the patients were instructed to enter every nasal (rhinorrhea, sneezing, obstruction) and conjunctival (lacrymation, itching, redness) symptom. The severity of symptoms was evaluated according to the following scoring: 0 = no symptoms; 1 = light; 2 = moderate; 3 = severe symptoms. The patients were also instructed to enter in the diary card the number of rescue medications (terfenadine 120 mg once a day). At the end of the study the patients were asked for an overall subjective evaluation of efficacy and safety of the treatment, claiming the following levels of improvement; 0 = poor; 1 = moderate; 2 = good; 3 = excellent. Statistical analysis has been done by non parametric test (Mann-Whitney U Test for paired comparisons).

RESULTS

During the treatment rare and light side effects have been recorded in No 6/15 (40%) patients of the incremental dosage group and No 6/22 (27%) patients of the constant dosage group, in all the cases limited to the administration site (sneezing).

Table III

Clinical efficacy of the two schedules during the pollen season

| | Incremental | Constant |
|---------------------|-------------|----------|
| Symptom score | 155 | 140 |
| Medication score | 9.8 | 13.0 |
| Overall evaluation: | | |
| tolerability | 1.8 | 2.1 |
| clinical efficacy | 1.8 | 1.8 |

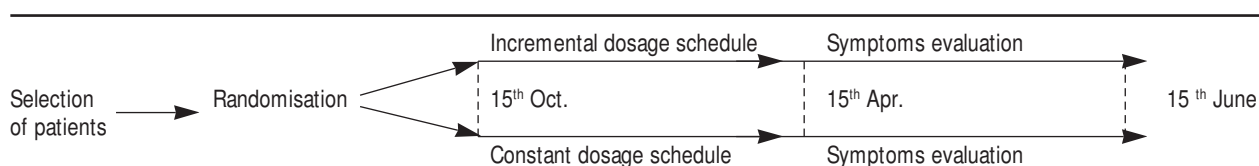
No systemic or bronchospastic reactions have been reported. All the patients completed the treatment. The totals of symptom and medications scores recorded during the pollen season are reported in table III. The mean symptom score resulted lower in the constant dosage group than in incremental dosage group (140.5 vs 155.2), while the first group took more rescue medications (13.0 vs 9.8). The overall subjective evaluation at the end of the study was better in the constant dosage group for tolerability during the treatment, while was the same for clinical efficacy during the season (table III).

DISCUSSION

The clinical efficacy of local nasal immunotherapy in grass pollen allergic rhinitis has been demonstrated by many double-blinded placebo-controlled studies, both with liquid extracts (3-13) and allergens in powder (14-24). Considering unquestionable the efficacy of this therapeutic treatment, we limited the present open randomised study to a comparison between the two dosage schedules. No significant difference have been reported as regards the symptom and medication scores during the pollen season and accordingly, no difference has been registered as regards the overall subjective evaluation (table II). As regards safety, it resulted optimal with both the schedules, being recorded few light and local side effects, lower in the

Table II

Study design



constant dosage group than in the incremental dosage one. The constant dosage treatment had the great advantage to be much more simple and to prevent dosage mistakes by the patients, which usually self-administer the treatment at home, therefore improving the compliance to the treatment. The surprising aspect of present study is the equivalence of the two treatments even through the mean cumulative dosage administered has been lower for the constant dosage than for the incremental one (3,000 vs 5,025 AU). The dosage chosen (40 AU) corresponds, as described in the Materials and Methods section, to the mean nasal provocative threshold. Evidently the repeated administration of this allergen amount has been sufficient to induce the immunological modifications reported in literature studies after local nasal immunotherapy, which can be briefly summarised in the following points:

— Reduction of the capacity of peripheral blood lymphocytes to proliferate when incubated with the specific allergen. This phenomenon has been observed after grass pollen nasal immunotherapy and was of the same degree of a parallel group of patients treated with injective immunotherapy, while was absent in the control group of untreated patients (26).

— Reduction of allergic inflammation at nasal levels after allergen challenge, demonstrated with a decrease of inflammatory cells (eosinophils and neutrophils) and epithelial expression of ICAM-1 adhesion molecules (19).

— Reduction of the provocative threshold in nasal specific provocation tests (14, 15, 17, 19-23).

In conclusion, the two treatment schedules could be considered equivalent. The constant dosage schedule could be preferred by the patients being easier to be administered and showing a better compliance to the treatment and a better tolerability profile.

RESUMEN

Historial: se ha comprobado y aceptado a nivel mundial la eficacia y seguridad de la inmunoterapia nasal a través de numerosas pruebas clínicas según el método controlado placebo. El tratamiento consiste en una fase de inducción a dosis crecientes seguida por una fase de mantenimiento. El objeto del presente estudio ha sido evaluar un nuevo programa de tratamiento más sencillo a dosis constantes.

Métodos y resultados: 26 pacientes afectados por rinitis alérgica a las gramíneas han sido tratados de acuerdo con una nueva posología constante, mien-

tras que 15 pacientes en un grupo de control han sido tratados de acuerdo con la posología convencional creciente. Una preparación comercial de alergenitos añadida al polvo (Allerkin®) y titulada en unidades biológicas (AU) ha sido utilizada para el estudio y suministrada utilizando un nebulizador nasal. La dosis acumulativa total suministrada según el tratamiento convencional ha sido mayor que en el tratamiento simplificado constante (5.025 frente a 3.000 AU). Para evaluar la eficacia, se han registrado la puntuación de los síntomas y medicación durante la primavera, la estación del polen, solicitando a los pacientes al final de la estación una evaluación subjetiva global. El análisis de la puntuación ha demostrado que ambos tratamientos resultaban equivalentes desde el punto de vista de la eficacia y seguridad, ya que los efectos colaterales se demostraban ligeros y limitados a la zona de administración (estornudos).

Conclusiones: el uso del producto a dosis constante es indicado para la administración de la inmunoterapia nasal ya que presenta la ventaja de una mayor sencillez. La prevención de errores de dosificación es importante en una terapia de autosuministración por parte de los pacientes.

Palabras clave: Rinitis alérgica. Alergia a las gramíneas. Inmunoterapia local nasal. Tratamiento a posología constante. Tratamiento a posología creciente.

Correspondence:

Prof. Luigi Andri
Via Giardino Giusti, 13
37129 Verona, Italy

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