ALLERGOL. ET IMMUNOPATHOL., 23, 5 (224-230), 1995

23472

Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study

V. Feliziani*, G. Lattuada, S. Parmiani***** and **P. .P. Dall'Aglio****

*Ambulatorio di Allergologia Divisione Medicina, Ospedale Civile di Lanciano. Chieti. Italia **Istituto di Patologia Medica - Scuola di Specializzazione in Allergologia ed Immunologia Clinica Università di Parma. Italia. ***Neo Abellò, Ospiate di Bollate, Milano, Italia.

SUMMARY

Thirtyfour patients suffering from rhinoconjunctivitis with or without asthma due to grass pollen, were submitted to sublingual immunotherapy according to a double blind placebo controlled experimental plan; eighteen patients received the active therapy, sixteen the placebo.

A rush preseasonal treatment schedule was followed in order to reach the maintenance dose in 15 days with two administrations per day; the top dose reached was then administered three times a week until the end of the pollen season.

The symptoms and drugs related to rhinoconjunctivitis and asthma were recorded by means of diary cards and grass pollen counts were performed during the season.

The actively treated group showed a reduction of symptoms of rhinoconjunctivitis and asthma and a lower intake of drugs for the same symptoms; all these differences resulted to be statistically significant.

No patient showed local or systemic side effects of any relevance.

According to these results of our study, sublingual rush immunotherapy is clinically effective and because of the ease of handling, the shortness of the treatment, the absence of relevant side effects and the high compliance of the patient can be considered as an alternative to classic injective immunotherapy in grass pollen allergic patients.

Key words: Sublingual immunotherapy. Grass pollen rhinoconjunctivitis. Rush immunotherapy.

Allergol. et Immunopathol., 23, 5 (224-230), 1995.

INTRODUCTION

The subcutaneous administration of allergen extracts for therapeutic purposes, commonly known as specific immunotherapy (ITS), was introduced more than 80 years ago and many double blind placebo controlled trials have proven its effectiveness (1-6).

In spite of the long and wide use, this procedure is not devoid of drawbacks, like the need of medical surveillance for at least 30 minutes after each injection (7), the possibility of local and/or systemic side effects (8), the non appearance of benefits before 6-12 months since the first injection.

In this situation, ITS will no longer be the first choice therapy for patients suffering from pollinosis of short duration; for children and for patients living far from Allergy Centers there is also a real problem of compliance, even if the prescription of ITS is correctly made.

Alternative, not injective, ways of administration of allergens involving a mucosal absorption have therefore been developed. Many clinical trials have studied gastric or enteric absorption of allergens, showing efficacy only with birch (9-11) and not with grasses even with very high dosages (12-15) or only after some years of treatment (16).

Good results have been obtained with intranasal allergen administration (17-21) but efficacy seems to be limited to rhinitis symptoms while a premedication is required before the allergen administration to overcome some uncomfortable minor local side effects.

Oral mucosa has been shown to be a very effective absorption site for drugs (22, 23); on the other hand, sublingual but not intragastric administration of an antigenic protein to rats gave a selective sup-

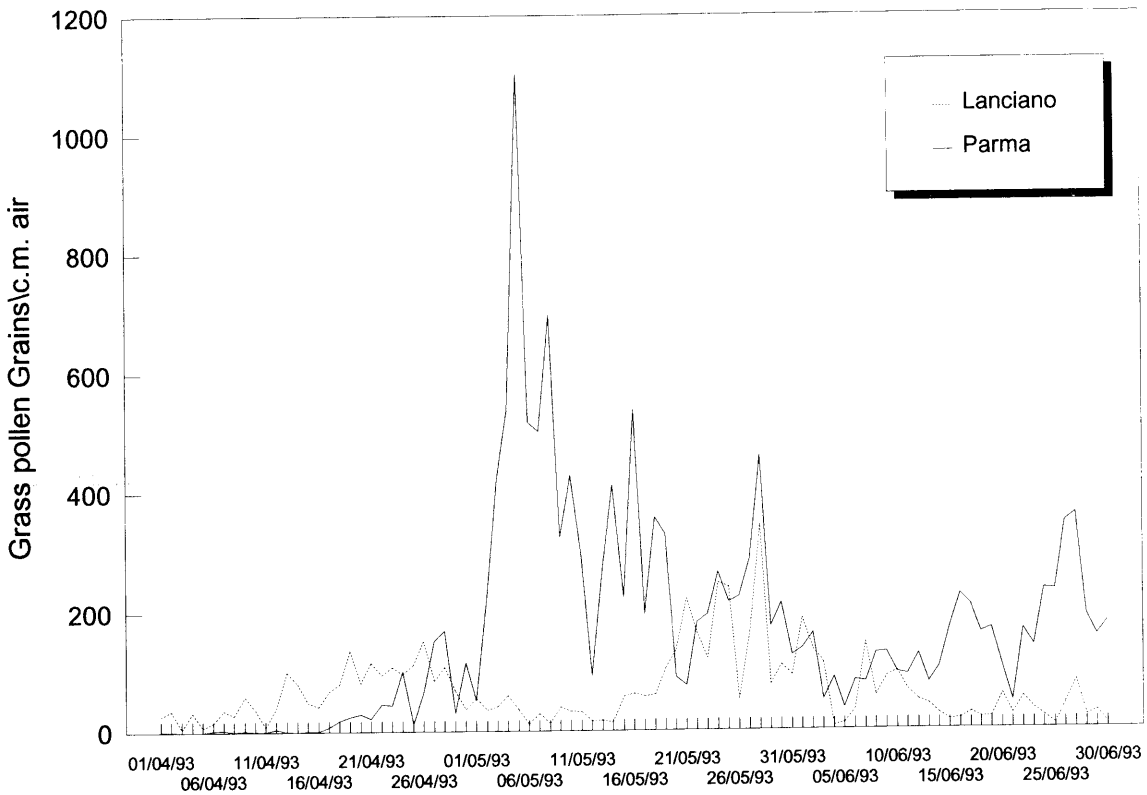


Fig. 1.—Grains/m^3 grass pollen in the air of Lanciano and Parma Spring-Summer 1993.

pression of IgE production (24), and a number of double-blind clinical studies in humans have shown safety and efficacy of the sublingual route with different allergens (25-29).

Sublingual immunotherapy (SLIT) is already being clinically used, in selected patients, in some European countries for some years; dosage schedules generally allow to reach the top dose in 30 days, with a preseasonal maintenance.

The dosage schedule, as for injective treatment, has been established on an empiric basis, leaving room for trials aimed at optimizing tolerance, safety, efficacy, compliance, through changes of frequency and quantities of allergen administrations.

The present study is based on this rationale and aims at investigating efficacy and safety of a SLIT performed with a grass extract administered according to a rush schedule («r»SLIT) so as to reach the top dose when the pollen season starts, according to a double blind placebo controlled plan.

The rush procedure, already being used for injective therapy in order to induce in a few days a rapid immunologic tolerance (30-32), has been chosen to shorten the treatment period before the pollen season.

All patients enrolled were allowed to use on request the symptomatic drugs included in the experimental protocol, giving an adequate therapy to everyone.

The present study represents the double blind placebo controlled check of a similar, open study, performed previously (33).

MATERIAL AND METHODS

Patients selection

34 patients have been selected according to the following:

— Inclusion criteria: age from 14 to 48 years; allergy only to grass pollen with in vivo (prick test) and/or in vitro (RAST) positive diagnosis; at least two years of oculo-rhinitis with or without asthma, clearly related to the grass pollen season.
— Exclusion criteria: serious asthma; nasal polyps; pregnancy; continuous treatment with steroids; chronic diseases of airways; auto-immune diseases; specific immunotherapy in progress or interrupted less than 5 years before; lack of compliance

Each patient was informed about aims and procedures of the trial and gave his written consent to take part.

The selection took place in two Allergy Centers; 14 patients have been enrolled in Parma and 20 have been enrolled in Lanciano (Ch).

All of them completed the trial.

Diagnosis

Prick tests were performed with a biologically standardized extract of pollen of 5 grasses (Dactylis glomerata, Lolium perenne, Festuca pratensis, Phleum pratense, Poa pratensis) with a potency of 100 BU/mL (34,35) (Neo Abellò, Milan, Italy). A wheal size equal or larger than that obtained with histamine 10 mg/mL was judged as positive. Specific IgE level was determined according to the RAST EIA technique (Pharmacia Diagnostics AB, Uppsala, Sweden), class 3 at least.

Slit

The active specific immunotherapy consisted of a biologically standardized extract of 5 grasses as above, graded into six strengths: 0.04; 0.2; 1; 5; 25; 100 BU/mL. The allergen solution contained 50% V/V of glycerol and 0.4% W/V of phenol as preservative in physiological saline (Neo Abelló, Milan, Italy).

The placebo was prepared in identical vials with the same appearance, colour, taste, but without the allergens.

Treatment schedule

The patients have been submitted to the treatment according to a double blind placebo plan. Each therapy was coded according to a key unknown to the clinician and to the patient and was assigned at random to each patient. A schedule of rush pre-seasonal treatment was followed, with drops to be taken sublingually twice a day, between meals, starting from 1 drop of the strength 0.04 BU/mL up to 5 drops of the same vial and then repeating the same procedure up to 5 drops of the strength 100 BU/mL or the maximum lower dose well tolerated.

The treatment was started in each Allergy Center so as to reach the maximum dose immediately before the grass blooming season. A co-seasonal maintenance treatment then followed with the top dose reached (on average 5 drops of the strength 100 BU/mL, corrresponding to about 20 BU) to be taken 3 times a week until the end of the pollen season. To exclude therapeutic or side effects linked to an absorption by the intestines, the drops of allergen extract had to be kept under the tongue for at least 2 minutes without swallowing and then anything remaining in the mouth had to be spat out.

Patients were checked twice a week during the increase of dosages and then twice a month during the maintenance therapy.

Drugs

All patients were instructed and allowed to use, if necessary, the following symptomatic medications according to the type and severity of the disease:

— Antihistamine tablets (terfenadine).
— Nasal topic steroids (beclomethasone dipropionate).
— Beta 2 bronchial topic (salbutamol).

Control parameters

Drug and symptom scores

All patients had to fill in a diary for the daily evaluation of symptoms during the grass pollen season, i.e. from the beginning of April to the end of June in Lanciano, from the middle of April to the end of July in Parma.

The symptoms had to be reported according to a 0-3 scale (0=no symptoms, 3=severe symptoms), and covered nasal symptoms (itching, sneezing, nasal discharge, nasal obstruction), eye symptoms (itching and redness of eyes), cough, symptoms of bronchial obstruction, wheezing.

At the same time they had to note down the possible use of drugs to which a specific daily score was given.

Grass pollen count

The concentration of grass pollen in the air of Lanciano and Parma was determined by means of collection through a volumetric sampler (VPPS 2000 in Lanciano and Burkard sampler in Parma). Data is shown in fig. 1 as number of grains per cubic meter of air.

Statistics

The Mann-Whitney U test was used to compare the score of symptoms and drugs used, registered in the diary of the patients, of the active group and of the placebo group respectively.

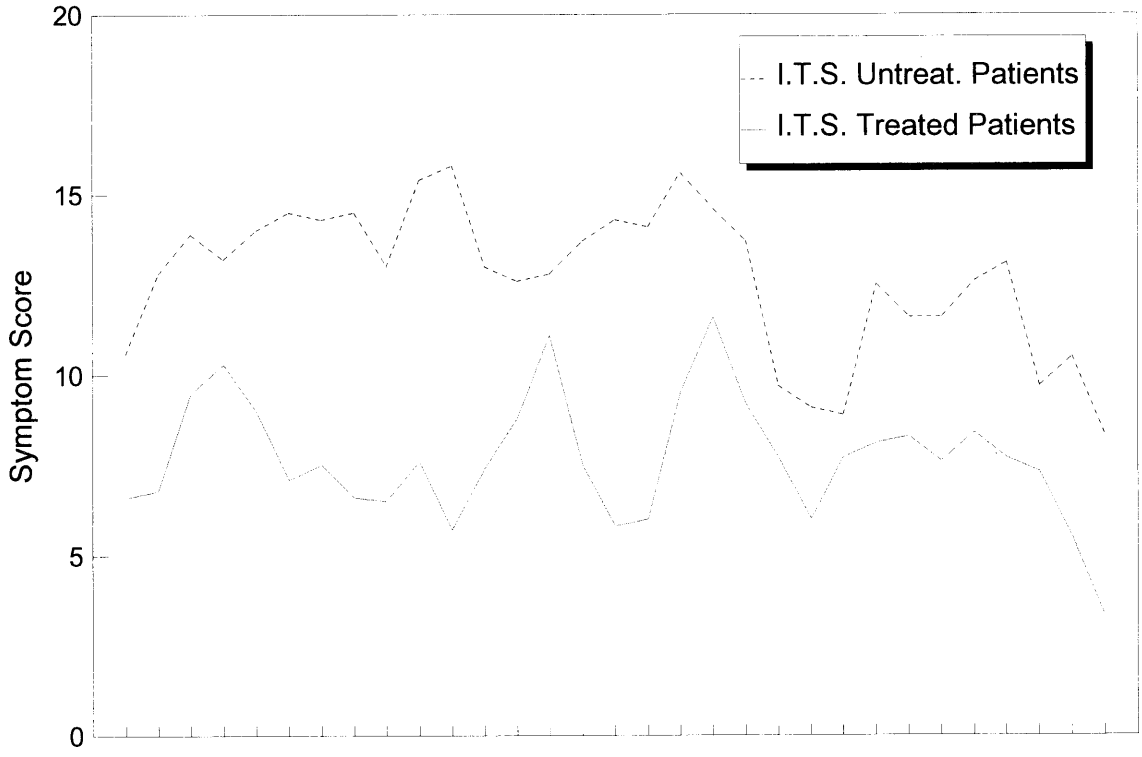


Fig. 2.—Symptom score of patients during the highest period of pollen season (from 1st to 31 May for Parma and from 15 May to 14 June for Lanciano). p = 0,008 Mann-Whitney U-test.

RESULTS

When the code was broken, at the end of the trial, 16 patients resulted as belonging to the placebo group, while 18 resulted to have been treated with the active therapy. The two groups were checked for and resulted to be balanced for age, sex, number of asthmatic patients as classified when enrolled, severity of the disease.

No patient reported local or general side effects of any importance, either with placebo or with active therapy.

All patients were free from symptoms and didn't take drugs before the pollen season. During the pollen season they showed, according to diary cards, symptoms of rhinoconjunctivitis; asthmatic symptoms were shown by patients classified as asthmatic and also by patients who had seldom suffered previously any episodes of bronchial obstruction during the grass pollen season. As the pollen calendars of the two areas did not correspond, for obvious differences in the geographical, meteo-climatic and environmental conditions, the analysis was restricted to the highest period of pollen counts of each area, i.e. from 1st to 31 May for Parma and from 15 May to 14 June for Lanciano.

The group of patients treated with the active therapy obtained a lower score of symptoms and drugs taken during the pollen season, in comparison to the placebo group (figs. 2 and 3). During the observation period, placebo treated patients showed an average score of 209.4 for symptoms and 76 for drugs, while actively treated patients reached an average score of 109.7 for symptoms and 24.05 for drugs.

In details, the analysis of data shows a statistically significant difference for:

- Rhinoconjunctivitis symptoms (p= 0.010).
- Drug consumption for rhinoconjunctivitis symptoms (p= 0.002).
- Asthmatic symptoms (p= 0.026).
- Drug consumption for asthmatic symptoms (p= 0.049).
- Overall symptoms (p= 0.008).
- Overall drug consumption (p= 0.002).

All these figures show that sublingual rush immunotherapy performed according to a high dosage preseasonal schedule is effective in reducing symptoms and drug consumption in patients allergic to grass pollen, according to a double blind placebo controlled plan.

Mechanism of action

Immunologic tolerance is a well known phenomenon and it could be obtained through functional inactivation of antigen specific T cell clones and/or a

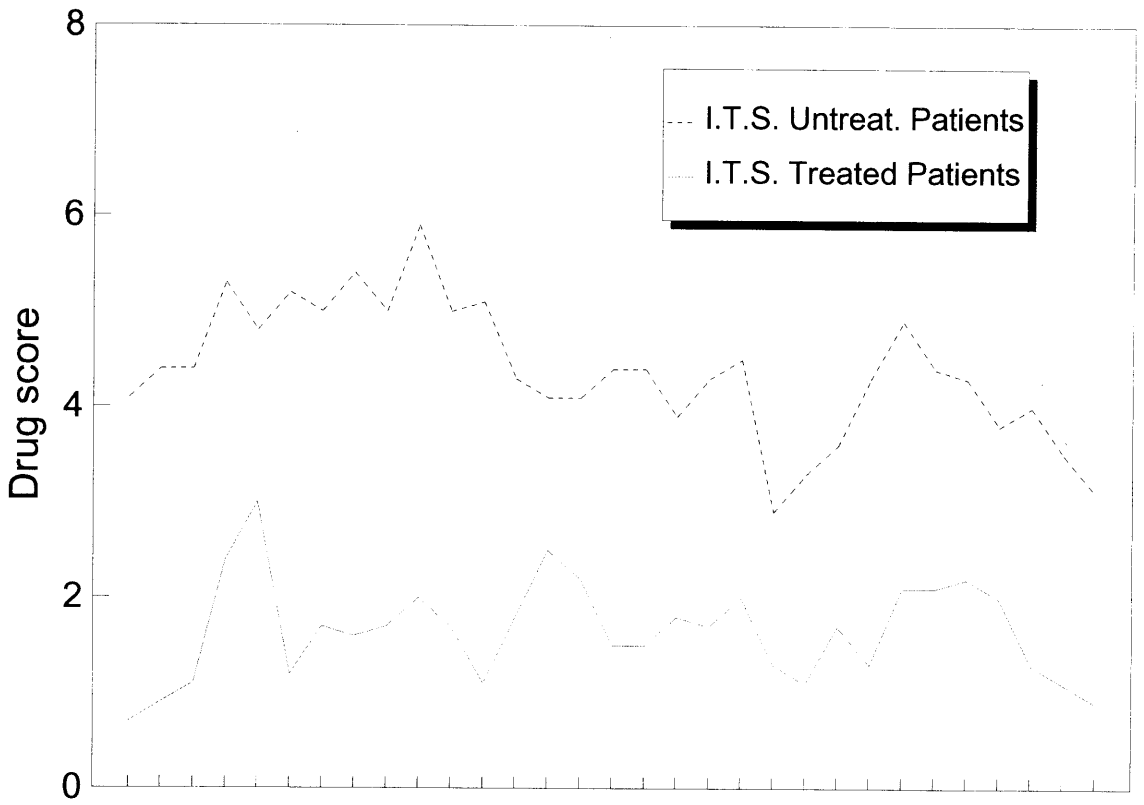


Fig. 3.—Drug score of patients during the highest period of pollen season (from 1st to 31 May for Parma and from 15 May to 14 June for Lanciano). P = 0,002 Mann-Whitney U-test.

reduction of the releaseability of basophils, according to data or hypothesis of some authors (23, 36-39).

This trial was planned only to show clinical benefits of «r»SLIT, if any, through the analysis of symptoms and drug consumption during the pollen season. Our data cannot therefore support any hypothesis of mechanism of action. On the other hand, we have not been able to show in our previous trial, with a similar but open plan, any change in IgE, total specific IgG and specific IgG4 (33), and clinical evaluations are judged as the only method which truly reflects clinical efficacy (7).

DISCUSSION

Only six double-blind placebo controlled studies report the results of sublingual immunotherapy in allergic patients (25-29, 40). Two of them investigated safety and efficacy of grass pollen extract treatment, reaching the evidence of clinical improvement for allergic rhinitis (28, 29).

In our double-blind placebo controlled trial, we have studied safety and efficacy of «r»SLIT in 34 patients suffering from rhinoconjunctivitis with or without asthma due to grass pollen, administering in the first 21 days an amount of allergen corresponding to the amount normally reached with 6 months of traditional preseasonal injective therapy performed with depot extracts of the same producer, according to the suggested schedule. Accordingly, 3 months of «r»SLIT mean an amount of allergen 6 times the amount of a preseasonal course of injective therapy. Considering this relative amount of allergen and that the allergen not absorbed was not swallowed but spat out, we can exclude any significative absorption of allergens by the digestive tract. Oral immunotherapy by the digestive route is said to require doses 50-200 times greater than those used for injective administration (9, 41).

The patients under active therapy showed a statistically significant lower level of symptoms for rhinoconjunctivitis and for asthma in comparison to the placebo group; these results are confirmed and stressed by a statistically significant lower level of medications for the same symptoms.

Symptoms and drug scores are otherwise in excellent agreement with pollen grains counts (fig. 4, Lanciano); a clear benefit from the active therapy could be seen already at the beginning of the pollen season, with a further improvement after one month of treatment, lasting until the end of the season.

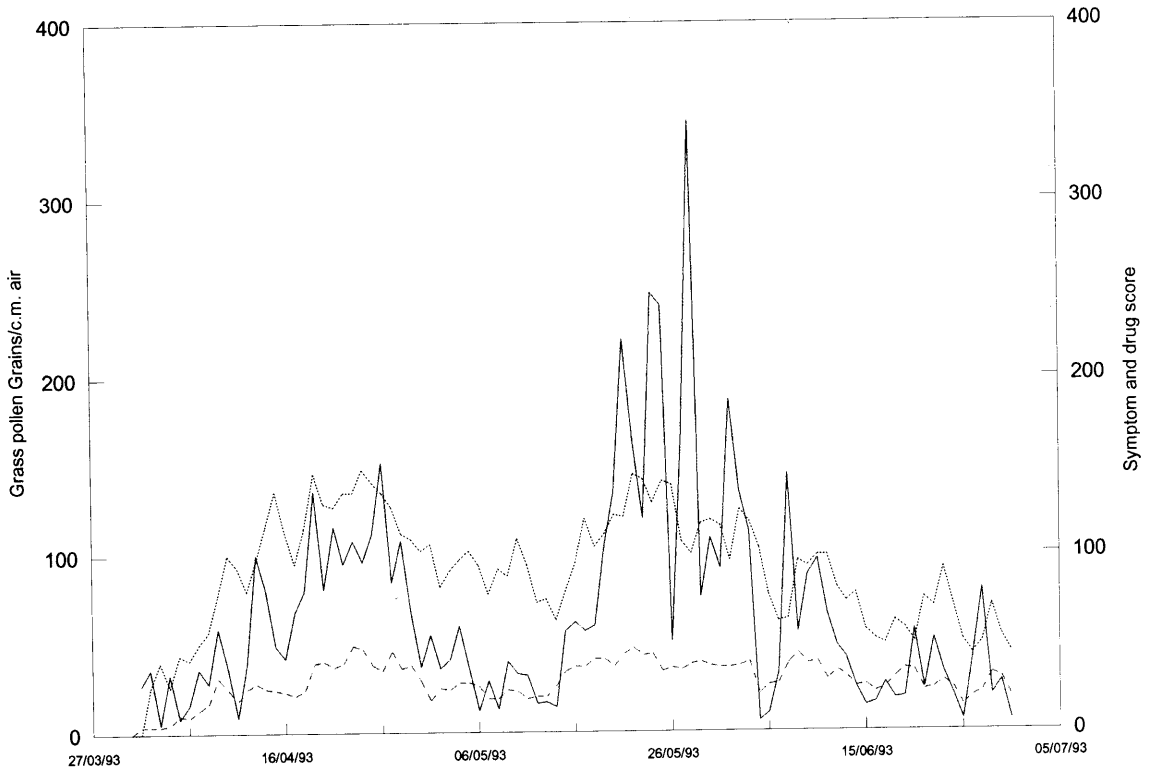


Fig. 4. Drugs (—) and symptom scores (...) of all patients in Lanciano, in comparison to the pollen counts (_).

With the classical injective immunotherapy, benefits are seen only some months after the first administration; in our case, clinical benefits were already obtained after only two weeks of treatment, without evident side effects.

This treatment can therefore be done in the patient's home, after adequate medical instructions, starting immediately before the pollen season.

«r»SLIT shows it self to be a simple, safe, clinically effective treatment for allergic symptoms due to grass pollen and can be considered as an alternative to the injective therapy for seasonal allergies such as pollinosis, mainly when the pollen season is short.

RESUMEN

Hemos realizado un estudio de inmunoterapia sublingual en 34 pacientes con rinitis sin o con asma por sensibilización a gramíneas según un diseño doble ciego placebo (18 pacientes recibieron un extracto constituido por una mezcla de 5 gramíneas y 16 el placebo). Se siguió una pauta de administración preestacional rápida de forma que la dosis de mantenimiento se alcanzó en 15 días; esta dosis se administró 3 veces por semana hasta el final de la época de polinización.

Durante la estación polínica se siguió un control de síntomas y medicación en relación al recuento de pólenes.

El grupo tratado con extracto mostró una reducción de síntomas y consumo de medicación que resultó ser significativa respecto al grupo placebo.

En base a los resultados obtenidos en nuestro estudio, consideramos que la inmunoterapia sublingual es eficaz y puede constituir una alternativa a la inmunoterapia convencional en el tratamiento de los pacientes polínicos por su sencillez de manejo, rápida respuesta, ausencia de reacciones adversas y el alto grado de colaboración del paciente.

Palabras clave: Inmunoterapia subliingual. Polinosis.

BIBLIOGRAPHY

1. Price J.F., Warner J.O., Hey E.N., Turner M.W., Soothill J.F. A controlled trial of hyposensitization with absorbed Dermatophagoides pteronyssinus antigen in childhood asthma. *Clin Allergy* 14: 209, 1984.
2. Malling H.J., Dreborg S., Weeke B. Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with Cladosporium herbarum. *Allergy* 41: 507, 1986.
3. Reid M.J., Moss R.B., Hsu Y-P, Kwasnicki J.M., Commerford T.M. Nelson B.L. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. *J. Allergy Clin. Immunol* 78: 590, 1986.

4. Bousquet J., Hejjaoui A., Clauzel A.M., Guerin B., Dhivert H., Skassa-Brociek W., Michel F-B. Specific immunotherapy with standardized Dermatophagoides pteronyssinus extract. II. Prediction of efficacy immunotherapy. *J Allergy Clin Immunol* 82: 971, 1988.
5. Bousquet J., Maash H.J., Hejjaoui A., Skassa-Brociek W., Wahl R., Dhivert H., Michel F-B. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. III. Efficacy and safety of unfractionated and high-molecular-weight preparation in rhinoconjunctivitis and asthma. *J Allergy Clin Immunol.* 84: 546, 1989.
6. Horst M. Hejjaoui A., Horst V., Michel F-B, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. *J Allergy Clin Immunol.* 85: 460, 1990.
7. Allergy (suppl) 48, 1993.
8. Lockey R.F., Benedict L.M., Turkeltaub P.C., Bukantz S.C. Fatalities from immunotherapy (IT) and skin testing (ST). *Allergy Clin Immunol* 79, 1987.
9. Bjorksten B., Moller C., Broberger U., Ahlstedt S., Dreborg S., Johansson S.G.O., Juto P., Lanner A. Clinical and immunological effects of oral immunotherapy with a standardized birch pollen extract. *Allergy* 41: 290-5, 1986.
10. Moller C, Dreborg S., Einarsson R. Cross reactivity between trees during immunotherapy. II. Specific IgE and IgG responses. *Clin Allergy* 17: 551-62, 1987.
11. Taudorf E., Laursen L.C., Lanner A., Bjorksten B., Dreborg S., Soborg M., Weeke B. Oral immunotherapy in birch pollen hay fever. *J Allergy Clin Immunol* 80: 153-61, 1987.
12. Cooper P.J., Darbyshire D., Nunn A.J., Warner J.O. A controlled trial of oral hyposensitization in pollen asthma and rhinitis in children. *Clin Allergy* 14: 541-50, 1984.
13. Mosbech H., Dreborg S., Madsen F., Ohlsson H., Stahl Skov P., Taudorf E., Weeke B. High dose grass pollen tablets used for hyposensitization in hay fever patients. A one-year double-blind placebo-controlled study. *Allergy* 42: 451-5, 1987.
14. Taudorf E, Weeke B. Orally administered grass pollen. *Allergy* 38: 561-4, 1983.
15. Trede N.S., Urbanek R. Combination of parenteral and oral immunotherapy in grass pollen allergic children. *Allergy* 44: 272-80, 1989.
16. Giovane A.L., Bardare M., Passalacqua G., Ruffori S., Scordamaglia A., Ghezzi E., Canonica G.W. A three-year double-blind placebo-controlled study with specific oral immunotherapy to Dermatophagoides: evidence of safety and efficacy in paediatric patients. *Clin Exper Allergy* 24: 53-59, 1993.
17. Deuschl H., Johansson S.G.O. Hyposensitization of patients with allergic rhinitis by intranasal administration of chemically modified grass pollen allergen. A pilot study. *Acta Allergol.* 32: 248-64, 1977.
18. Georgitis J.W., Nickelsen J.A., Wypych J.I., Barde S.H., Clayton W.F., Reisman R. E. Local intranasal immunotherapy with high-dose polymerized ragweed extract. *Int Arch Allergy Appl Immunol* 81: 170-3, 1986.
19. Johansson S.G.O., Deuschl H., Zetterstrom O. Use of glutaraldehyde-modified timothy grass pollen extract in nasal hyposensitization treatment of hay fever. *Int Arch Allergy Appl Immunol* 60: 447-60. 1979.
20. Mehta S.B., Smith J.M. Nasal hyposensitization and hay fever. *Clin Allergy* 5: 279-84, 1975.
21. Nickelsen J.A. Goldstein S., Mueller U., Wypych J., Reisman R.E., Arbesman C.E. Local intranasal immunotherapy for ragweed allergic rhinitis. I. Clinical response. *J. Allergy Clin Immunol* 68: 33-40, 1981.
22. Benet L.Z., Sheiner LB. Pharmacokinetics: the dynamics of drug absorption, distribution and elimination. In: Gilman A.G., Goodman L.S., Rall T.W., Murad F., eds. The pharmacological basis of therapeutics. 7th edn. New York: *MacMillan Publishing Co*: 1985: 7.
23. Challacombe S.J., Tomasi T.B. Systemic tolerance and secretory immunity after oral immunisation. *J Exp Med* 152: 1.459, 1980.
24. Holt P.G., Vines J., Britten D. Sublingual allergen administration. I. Selective suppression of IgE production in rats by high allergen doses. *Clinical Allergy* 18: 229-34, 1988.
25. Tari M.G. Mancino M., Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. *Allergol et Immunopathol*: 18: 5: 277-84, 1990.
26. Novembre E., Marano E., Bernardini R., Caria M., Dini L., Vierucci A. Studio controllato sull'immunoterapia per via sublinguale nell trattamento dell'asma allergico del bambino. *Riv Ita. Pediatr* 17: 75-78, 1991.
27. Scadding G.K., Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clinical Allergy* 16: 483-91, 1986.
28. Van Niekerk C.H., De Wet J.I. Efficacy of grass-maize pollen oral immunotherapy in patients with seasonal hay-fever: a double-blind study. *Clinical Allergy* 17: 507-513, 1987.
29. Sabbah A., Hassoun S., Le Sellin J., Andrè C., Sicard H. A double-blind, placebo-controlled trial by sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy* 49: 309-313, 1994.
30. Antonicelli L, Pucci S., Sacchi G., Migliorini G., Bonifazi F. Safety of rush immunotherapy protocol with a standardized Dt Pteronyssinus extract. *Clin Exp Allergy* 20 (supp.) 108, 1990.
31. Armentia-Medina A., Blanco-Quiros A., Martín Santos, J.M. Alvarez Cuesta E., Moneo I., Carreira J., Losada E. Rush immunotherapy with a standardized Bermuda grass pollen extract. *Ann Alergy* 63: 127-135, 1989.
32. Bousquet J, Hejjaoui A., Skassa-Brociek W., Guerin B., Maasch H.J. Dhivert H., Michel F.B. Double-blind, placebo controlled immunotherapy with mixed grass pollen allergoids. Rush immunotherapy with allergoid and standardized orchard grass pollen extract. *J. Allergy Clin Immnonol* 80, 591, 1987.
33. Feliziani V., Marfisi R.M., Parmiani S. Rush immunotherapy with sublingual administration of grass allergen extract. *Allergol et Immunopathol.* 21: 5: 173-178, 1993.
34. Brighton W.B. Topping M.D., Henocq E. Activity units for allergen extracts. *Clin Allergy* 9: 591-596, 1979.
35. Carreira J., Rubio M., Herrero T., Horak F., Businco L., Wuthrich B., Bearzi De Prada V., Berry J.B., Lischka G., Brighton W.D. Collaborative clinical assay of the biological potency of allergen skin-test extracts. *Clin Allergy* 14: 503-507, 1984.
36. Brandtzaeg P. Immune function of human nasal mucosa and tonsils in health and disease. In: Bienenstock J. ed. Immunology of the lung and upper respiratory tract. *New York: McGraw Hill*, 28-95, 1984.
37. Mendoza G.R., Minagawa K. Subthreshold and suboptimal desensitization of human basophilis. *Int Arch Allergy Appl Immunol* 68: 101-7, 1982.
38. Sobotka A.K., Dembo M. Antigen specific desensitization of human basophilis. *J Immunol* 122: 511, 1979.
39. Tomasi T.B. Oral Tolerance. *Transplantation* 29: 353-6, 1980.
40. Nelson H.S., Oppenheimer J., Vatsia G.A., Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *JACI* 92: 229-36, 1993.
41. Duan S.Q., Fu Y.X., Leng X., Ye S.T. A double-blind trial of oral immunotherapy for Artemisia pollen asthma with evaluation of bronchial response to the pollen allergen and serum-specific IgE antibody. *Ann Allergy* 64: 27-31, 1990.

Correspondence:

Dott. Silvano Parmiani
NeoAbellò
Via Falzarego, 8
20021 Ospiate di Bollate, Milano (Italia)