A double-blind, placebo-controlled study of preventive immunotherapy with E.P.D., in the treatment of seasonal allergic disease.

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Résumé

De nos jours, on recommande un contrôle des symptômes saisonniers par une immunothérapie préventive et facile à utiliser (une injection intradermique huit semaines avant le pic pollinique suffit).

Nous avons vérifié l'efficacité clinique de l'EPD (Enzyme Potentiated Desensibilization) dans une étude en double aveugle versus placebo. Cette immunothérapie particulière consiste en une injection intradermique d'un mélange constitué d'extraits d'allergènes en doses extrêmement basses et d'une enzyme , le bêta-glucuronidase. Le vaccin est administré une fois par an, huit semaines avant le pic pollinique.

Nous avons étudié un groupe de 40 patients allergiques au pollen de graminées. Les résultats statistiquement analysés sur la base d'une échelle des symptômes, ont montré une bonne efficacité clinique et une réduction significative de la consommation de médicaments durant la haute saison pollinique.

En raison de l'efficacité clinique, de l'administration aisée et de l'excellente tolérance de l'immunothérapie, l'EPD est particulièrement indiquée pour prévenir les symptômes saisonniers chez les patients allergiques aux Graminées.

Mots-clés : EPD - Immunothérapie préventive - Prévention des allergies - Graminées - Bêta-glucuronidase.

Summary

Control of seasonal symptoms by means of a preventive and easy to use (only one intradermal injection eight weeks before the pollen peak) immunotherapy, is recommended nowadays.

We verified the clinical efficacy of E.P.D. (Enzyme Potentiated Desensibilization) in a double-blind, placebo-controlled study. This particular immunotherapy consists of an intradermal injection mix, made up of allergenic extracts at extremely low doses and an enzyme called beta-glucuronidase. The vaccine is administered once a year, eight weeks before pollen peaks.

We studied a group of 40 patients allergic to grass pollen.

The results, analysed statistically on the basis of a symptoms score, showed good clinical efficacy and a significant reduction of drug consumption during the high pollen period.

Due to the clinical effectiveness, easy administration (only one injection) and excellent tolerance of the immunotherapy, E.P.D. is particularly suited for the prevention of seasonal symptoms in patients allergic to grass pollen.

Key-words : E.P.D., Preventive immunotherapy - Allergy prevention - Grass - Beta-glucuronidase.

INTRODUCTION

Immunotherapy with E.P.D. (Enzyme Potentiated Desensibilization) vaccine is a relatively new method for treating IgE-mediated allergies, asthma, conjunctivitis, and oculo-rhinitis.

The group used the E.P.D. administered intradermally, and results demonstrated only 1 dose are needed to obtain a clinical improvement.

The vaccine consists of two components that are prepared extemporaneously and injected intradermally. One component is made up of small quantities of several aero-allergens and includes the most common pollens, dust mites, several moulds, and dandruff.

The second component is an enzyme beta-glucuronidase which has been purified, pre-treated and activated to work as an adjuvant to the immune system.

Some clinical trials which have been carried out confirmed the effectiveness of the E.P.D. in the reduction of seasonal symptoms and the consumption of symptomatic drugs (7, 8, 9, 10, 11).

More recently an increase of the IL10 and the IL6 (F. Ippoliti personal communication) has been observed, after treatment with E.P.D.

This method of treatment differs from traditional specific immunotherapy (SIT) where vaccines are injected subcutaneously or administered orally or intranasally. In fact, SIT uses extracts with much higher doses of allergens that are gradually increased to induce persistent tolerance to the allergens (12).

The traditional immunotherapy is specific for an allergen and its objective is to favourably alter the natural

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history of the illness, whereas the E.P.D. is proposed to prevent the symptoms of the allergies.

Although S.I.T. has been used for more than eighty years, today its effectiveness is widely accepted but we still have to understand how it works and the discussion is not yet complete. E.P.D. treatment has only been used for the past ten years and we believed the best approach was to reconfirm the effectiveness of this simple immunotherapy, which is the first one able to prevent the allergic seasonal symptoms from grasses, with a double blind study.

MATERIALS AND METHODS

DESIGN OF THE STUDY

A double-blind, placebo-controlled study : the times and the methods are shown in figure 1.

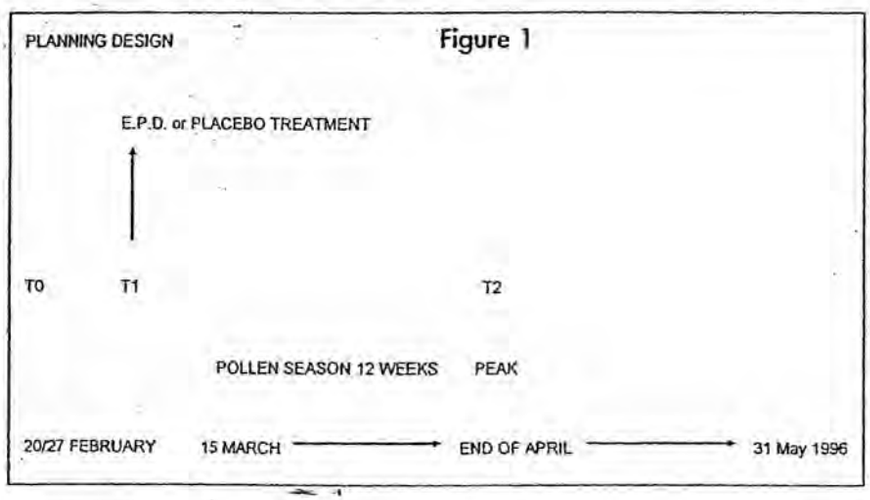


Figure 1

POPULATION AND AIM OF THE SURVEY

Forty patients (20 m, 20 f) between 18 and 40 years of age (average age : 27 years and 4/12 months) were involved in the study.

All patients were allergic only to grasses and suffered from seasonal rhinoconjunctivitis and were not previously undergoing treatment with a specific immunotherapy.

The allergy diagnosis was made on the basis of the medical history, prick tests and the dosage of IgE-specific serum, with 3rd and 4th class positivy according to the standards presented by the international consensus report on the diagnosis and management of rhinitis (13).

The patients were divided into two groups :

Group 1 patients were given the E.P.D. immunotherapy and Group 2 the placebo, the latter was prepared in identical packages to the former, but the placebo treatments were prepared with physiological solution, 50% of them have also histamine (HCl) to the final concentration of 0,1 mg/ml 0,54 mmol/l.
The addition of histamine was considered necessary for the double blind study, as it is known that the active treatment can sometimes cause modest local reactions.

PREVENTIVE IMMUNOTHERAPY

An extemporaneous mix of 0.05 ml of E.P.D. (S.A.R.M. - Guidonia - Rome, Italy) composed of 0.01 ml of a beta-glucuronidase solution (corresponding to 40 Fishman Units) and 0.04 ml of allergenic extracts (1 Noon Units, corresponding to 0.02 B.U. of each allergen : grass, Parietaria o., Olea e., Artemisia a., Birch a., Cladosporium h., Aspergillus f., Alternaria a., Dermatophagoides p., cat and dog's dander ; cyclohexanediol 50 pg. ; protamine sulphate 50 ng ; chondroitin sulphate 30 pg) were administered during active therapy. The beta-glucuronidase is of molluscan origin and was purified by column chromatography (Seravac Ltd, Johannesburg).

A solution containing no active ingredients was administered in the placebo treatment given to the control group. The vaccine was injected intradermally during the last week of February 1996, 8 weeks before the period of maximum pollination (April 96).

SYMPTOMATIC MEDICATION

The daily taking of an oral antihistamine was recommended for the pharmacological control of the symptoms during the season time. The employment of antihistamine were recorded in the diary patients to assist in the evaluation of the effectiveness of the immunotherapy.

EVALUATION CRITERIA

■ **Symptom and medication scores**

All patients were monitored by means of clinical and medication scores and were studied for 13 weeks from March 15 to May 31 1996, since the number of pollen granules per cubic meter reaches up to 40 during this period.

Patients were asked to keep a daily record of the presence and grade of nasal and ocular symptoms. The nasal symptoms included early morning and daytime obstruction, nasal itching, sneezing, rhinorrhea.

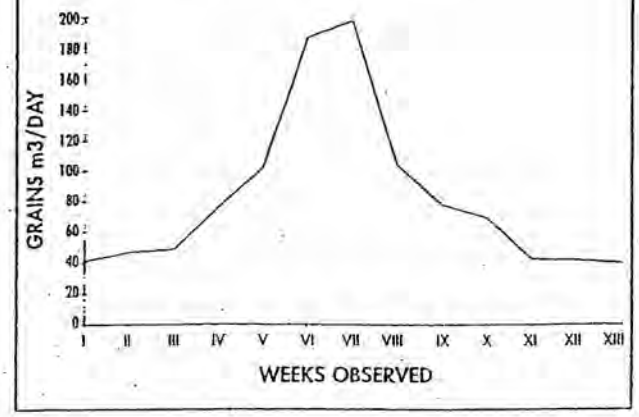
The ocular symptoms included itching, reddening, photophobia and sensation of a foreign body. The above symptoms were graded as follows : 0 absences of symptoms, 1 : mild, 2 : moderate, 3 : severe.

The daily oral intake of antihistamines was recorded on the same diary card.

■ **Pollen counts**

A total daily count of the grass pollen detected in the area of L'Aquila with a Buckard volumetric collector was carried out during the 13 weeks from March 15 to May 31 1996 (figure 2). Data were expressed as the weekly average of pollen grains/m3/day of air.

Figure 2 : Pollen counts



STATISTICAL ANALYSIS

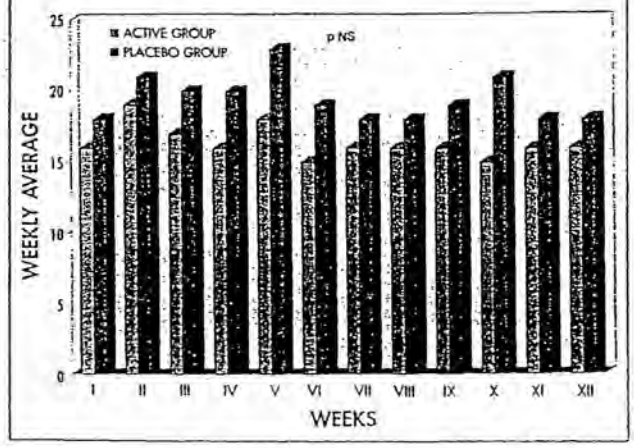
To evaluate the symptoms and drug intake scores we employed the Wilcoxon test. Probabilities <0.05 were considered significant. The statistical study was carried out on days of maximum pollen counts (from 5 April to 17 May) to evaluate both symptoms and medication. Both groups were homogeneous.

RESULTS

All patients completed the study without any side effects.

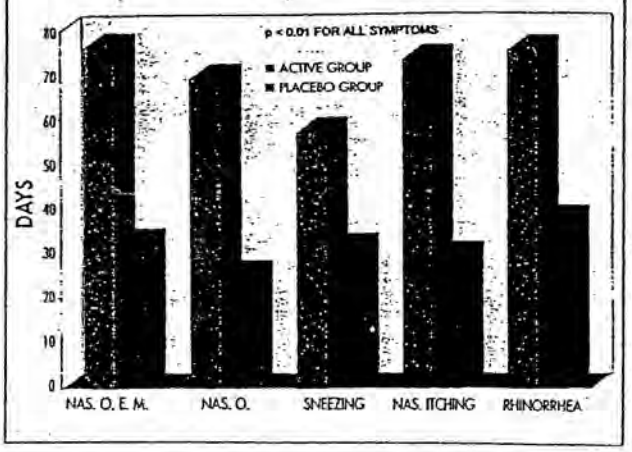
A score comparison from 15 March to 31 May 1996 showed a reduction in the clinical scores of E.P.D. treated patients (figure 3) even though this was not significant.

Figure 3 : Symptoms score



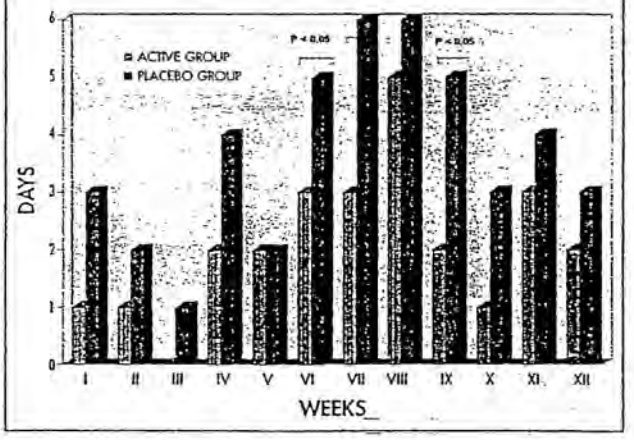
The clinical effectiveness was confirmed by calculating the days without symptoms ; the patients not treated had more symptom free days than those treated (p<0,005 for all symptoms analysed) (figure 4).

Figure 4 : Days without symptoms



Furthermore the efficacy of E.P.D. was illustrated by the reduced consumption of antihistamine drugs. We evaluated how many days patients did not use these drugs and noted that there was a significative reduction in the treated group during the high pollen season (figure 5).

Figure 5 : Antihistamine score



CONCLUSIONS

The main treatment of seasonal oculo-rhinitis is specific immunotherapy but frequently there are no prior indications which means that many patients have to take preventive or symptomatic drugs.

Today control of seasonal symptoms using a preventive and easy to use immunotherapy (only one intradermal injection eight weeks before the pollen peak) is recommended.

Some authors have shown the overall clinical effectiveness of the E.P.D. treatment and we believe our study confirms these results.

At the end of February (as recommended by the manufacturer) we treated patients allergic to grass and found that this simple treatment was sufficient to obtain a good clinical improvement.

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But how does it work ? We believe that this question is also applicable to traditional immunotherapy, and E.P.D. is too recent to give us a complete response to the question. Recently, an IL-6 and IL-10 increase has been observed in treated patients, and authors have suggested that the adjuvant role of the beta-glucuronidas in presenting the allergens to dermal antigen presenting cells is able to induce allergenic tolerance (14). Consequently E.P.D. immunotherapy is a particularly interesting method and the lack of significant side effects makes the benefit/risk ratio particularly favourable.

Our double-blind, placebo-controlled study confirms the clinical benefits of the preventive immunotherapy.

However, future studies are needed to evaluate the immunologic parameters to gain understanding of the mechanism which triggers of the action of this new immunotherapy.

REFERENCES

1. L.M. MCEWEN, M.A. GANDERTON, C.W.M. WELSON AND J.H.D. BLACK. - Hyaluronidase in the treatment of allergy. Brit. Med. J., 509-530, 1967.

2. L.M. MCEWEN AND M.S. STARR. - Enzyme potentiated hyposensitization I. The effect of pretreatment with beta glucuronidase, hyaluronidase and antigen on anaphylactic sensivity on guinea pigs, rats and mice. Int. Arch. Allerg., 42, 152-158, 1972.

3. L.M. MCEWEN. - Enzyme potentiated hyposensitization II. Effect of glucose, glucosamine, N-acetylamino-sugars and gelatin on the ability of F Beta glucuronidase to block the anamnestic response to antigen in mice. Ann. Allerg., 31, 79-83, 1973.

4. L.M. MCEWEN, M. NICHOLSON, I. KITCHEN AND W. SHEILA. - Enzyme potentiated hyposensitization III. Control by sugars and diols of immunological effect of beta glucuronidase, in mice and patients with hay fever. Ann. Allerg., 31, 543-550, 1973.

5. L.M. MCEWEN, M. NICHOLSON, I. KITCHEN, J. O'GORMAN AND W. SHEILA. - Enzyme potentiated hyposensitization IV. Effect of Protamine on the immunological behavior of beta glucuronidase in mice and patients with hay fever. Ann. Allerg., 34, 290-295, 1975.

6. L.M. MCEWEN. - Enzyme potentiated hyposensitization V. Five case reports of patients with acute food allergy. Ann. Allerg., 35, 99-103, 1975.

7. P. FELL AND J. BROSTOFF. - A single dose desensitization for summer hay fever. Results of a double blind study - 1988. Eur. J. Clin. Pharmacol., 77-79, 1990.

8. J. EGGER, A. STOLLA, L.M. MCEWEN. - Controlled trial of hyposensitization in children with food-induced hyperkinetic syndrome. The Lancet 339, 1150-53, 1992.

9. G.A. VENA, G. CURATOLI, V. D'ARGENTO AND G. ANGELINI. - POLLINOSIS : A new immunotherapeutic methodology. The Med. J. of Surg. and Med. 253-256, 1993.

10. G. CARAMIA, F. FRANCESCHINI, A. CIMARELLI, M.S. CIUCCHI, R. GAGLIARDINI AND E. RUFFINI. - The efficacy of E.P.D., a new immunotherapy in the treatment of allergic diseases in children. Allergie et Immunologie, 28, 70-73, 1996.

11. A. CANTANI, V. RAGNO, M.A. MONTELEONE, P. LUVENTI, L. BUSINCO. - Enzyme-potentiated desensitization in children with asthma and mite allergy : A double-blind study. J. Invest. Allergol. Clin. Immunol., 6 (4), 270-276, 1996.

12. EAACI Immunotherapy position paper. 1993, Weeke HJ and B editors. Allergy, 48, 28, 1993.3.

13. International rhinithis management working group : International consensus report on the diagnosis and management of rhintis. Allergy 49, suppl. 19, 1994.

14. A.H. ENK., J. SALOGA, D. BECKER. - B1P6 madzadeh M. Knop J. - Induction of hapten-specific tolerance by interleukin 10 in vivo. J. Exp. Med. 179 (4), 1397-1402, 1994.