

Does the effect of immunotherapy last after termination of treatment?

Follow-up study in patients with grass pollen rhinitis

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In a previous study, 39 adults with grass pollen allergy were hyposensitized for approximately 2 1/2 years. Treatment was performed in a double-blind fashion with extract made from timothy grass - either Alutard SQ 20-component extract or a purified 2-component extract, including only the two major allergens *Phl p* V and VI. Standardized symptom + medicine scores and challenge tests demonstrated a clinical effect, most markedly in the group receiving 20-component extract. Six years after termination of treatment, 38 patients could be approached and 16 in each group were examined and repeated symptom scoring during the subsequent season. When adjustment for variations in pollen counts were made, medicine + symptom scores stayed low during the follow-up period. Specific IgE-antibodies against timothy showed an increase to initial values during the same period, whereas total IgE antibodies remained low. Skin prick test reactions with timothy allergen tended to increase but were still smaller than before treatment. Retrospectively, the patients reported symptoms to have stabilized or even further decreased after termination of treatment, with no significant difference between groups. In conclusion, the clinical effect was still present more than 6 years after termination of treatment. Some *in vitro* parameters tended to return to pretreatment level. The spontaneous course of the disease in non-hyposensitized patients was not investigated.

Key words: follow-up; grass pollen; hay fever; IgE, immunotherapy; RAST.

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Immunotherapy (IT) with pollen allergens has shown effective in several studies (4). The therapeutic effect has been demonstrated when maintenance dose is reached but little is known concerning the optimum duration of treatment and the duration of the therapeutic response obtained. The regional variation in the way IT is performed ranging from preseasonal to lifelong treatment illustrates our lack of knowledge within this field.

The aim of the present study was to investigate whether the therapeutic effect was still present 6 years after termination of IT. For this purpose, we re-tested a group of patients ini-

tially treated for grass pollen rhinitis with two standardized extracts.

MATERIAL AND METHODS

Design

The study was performed as a follow-up study of patients who had participated in one of the earliest controlled studies using immunologically standardized extracts for IT (13). In this previous investigation, half of the patients were treated with a partially purified timothy extract containing about 20 potential allergens out of the

extractable 30–45 timothy antigens (20-component extract). This proved to be more effective than a purified 2-component extract containing the timothy major allergens *Phl p* V and VI (Nos. 25 and 19) as evaluated by immunological and clinical parameters. Almost 6 years after termination of treatment, the patients were contacted by mail and asked to fill in a questionnaire describing the development in their disease. If possible, they were then offered an allergy testing in the clinic and were asked to record symptoms and medicine consumption in a diary card during the subsequent grass pollen season. The results from allergy tests and medicine + symptom scores were then compared with results obtained from the previous study.

Immunotherapy

Forty patients aged 15–43 years with hay fever for at least two grass pollen seasons (median: 9.5 years) were treated with IT from January 1978. Updated addresses were produced from the national register. One out of the 39 patients completing the IT was impossible to trace and subsequently 38 were approached preseasonally in 1986.

Half of the patients had received the 20-component extract (20-CE). The rest were treated with the 2-component extract (2-CE). All but one patient (receiving 2-CE) continued treatment up till preseason 1980, i.e. for 2 years and 4 months. Clinical and *in vitro* results from this trial are described elsewhere (10, 11, 12, 14).

Questionnaire

In the questionnaire the patients were asked to describe their hay fever symptoms during the period elapsed from pretreatment, i.e. summer 1977, up till present (i.e. preseason 1986). The answers should be given year by year in a semiquantitative way by graphically indicating the severity of symptoms relative to the pretreatment symptoms.

Diary cards

If possible, the patients were supplied with diary cards covering an identical 4-week period

June + July 1980, 1981 and 1986 (week Nos. 24–27), when maximum grass pollen in the air was expected. The cards were identical to those filled in during the IT trial and the same standard spectrum of medication was aimed at, avoiding prophylactic treatment (10). If symptoms occurred, the patients were instructed to take antihistamine tablets (dexchlorpheniramine, Polaramine® 2 mg) up to 4 times a day and if necessary to add eye drops containing antazoline sulphate 5% + naphazoline nitrate 0.25% (Antistina-Privin®). If the treatment was insufficient, the patients were given corticosteroid tablets (Prednisone 2.5 mg). Salbutamol (Ventoline®) aerosol 0.10 mg/puff was used if necessary. Medicine used was given scores as follows: 1 eye drop in one eye = score 1, 1 antihistamine tablet = score 2, 2.5 mg of Prednisone = score 3 and 1 puff of salbutamol = score 1.

Using a rating scale from 0 to 3, the patients were asked to describe seven possible allergy symptoms daily: nose running, nose blocking, sneezing, eye redness, eye itching, coughing and wheezing. Median scores per day were calculated taking into account possible reductions in recording periods due to journeys abroad, etc.

Diary cards from patients not able or willing to give up treatment with nasal spray containing corticosteroid were excluded from the analyses of scores.

Due to a considerable year-to-year variation in airborne grass pollen (Table 1), all symptom and medicine scores were adjusted to 1980 exposure level. This was done by dividing the score by the amount of pollen collected during the scoring-season and multiplying with the corresponding 1980 pollen count.

Pollen counts

Pollen grains were collected in a Burkard volumetric spore trap. Up to 1981 all patients were living within 40 km of the trap. In 1981 and in 1986 two of the patients had increased the distance to 200 km but regional differences have shown to be small in Denmark (16).

Skin prick test (SPT)

A biologically standardized timothy grass pollen extract reconstituted in glycerol 50 % (Soluprick®, Allergologisk Laboratorium AS, Copenhagen, Denmark) was used for SPT in 10-fold dilutions from 10 HEP/ml to 0.1 HEP/ml. Biological standardization had been performed by SPT, RAST-inhibition and immune electrophoresis for the batches used during IT and later. Histamine dihydrochloride 1 mg/ml acted as a reference. Tests were performed in singular with blood lancets except at the follow-up investigation. Due to changes in routines they were substituted by Dome Hollister Stiers lancets with 1 mm stylus in duplicate tests (15). Results were expressed as the lowest allergen concentration giving a weal area with a median diameter equivalent to the histamine reference prick as described (10).

Total IgE

Measurement of total serum IgE was performed by means of Phadebas PRIST® (2) according to the manufacturer's instructions. All analyses were performed in duplicate. At follow-up an identical technique was applied.

Allergen-specific IgE

Serum IgE directed against timothy grass was measured by Al-RAST (radioallergosorbent test) as described (6). Mean values from duplicate examinations were determined and the results were expressed in sorbent units (SU) - relative to the antibody-binding of a documented timothy pollen allergic patient. At follow-up an identical technique was applied.

Statistical methods

Mann-Whitney's or Wilcoxon's tests were employed using two-tailed tests with 5 % significance level.

RESULTS

Responses

Thirty-five of the 38 patients approached completed the questionnaire. Three patients did not

respond to our letter(s), one due to long-term stay abroad, two for unknown reasons. In three additional cases testing was not possible, one patient had moved to another region and two patients did not want to participate for other reasons. The remaining 32 patients (16 from each treatment group) were examined by SPT and antibody measurements preseasonally, and recorded symptom and medicine scores during the subsequent grass pollen season (1986). Instead of the study medication, two patients in each group preferred to continue prophylactic treatment with nose spray containing corticosteroid, since this was able to abolish their remaining symptoms almost totally. The patients did not differ from the rest of the group with regard to their retrospective assessment, initial scores (1980), or changes in allergen-specific and total IgE in serum.

Questionnaires

The retrospective all-in-all evaluation by questionnaires revealed symptoms to have stabilized or even further decreased in nearly all patients after termination of treatment - with no significant differences between groups (Fig. 1). The median symptoms for the 6th season after IT (1985) were 33 % and 38 % of the pretreatment values for the 20-CE and 2-CE treated, respectively. The therapeutic effect was seen in spite of a 10 % higher grass pollen exposure (Table 1). Three patients (19 %) in each group described their symptoms during the last season to be less than 10 % of the pretreatment level and in 30 of the 32, symptoms did not exceed 80 % during this season. Two patients described unchanged symptoms, one had no benefit of the treatment (2-CE) at all and the other had relapsed 1 year after termination of therapy with 20-CE.

Seasonal scores

Since no pretreatment scores were available, the adjusted medicine and symptom scores collected 6 years after IT were compared with the scores originating from the seasons at the termination of and 1 year after this treatment (1980 and

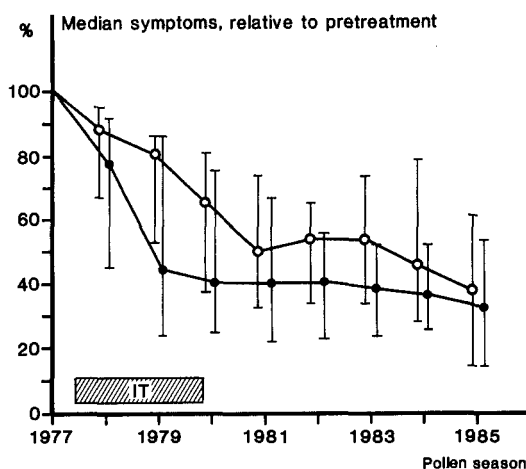


Fig. 1. Retrospective description of hay fever symptoms during and subsequent to immunotherapy relative to pretreatment level. Medians and quartiles are given for 2-CE (○) and 20-CE (●) treated groups.

1981). For the 2-CE group a further improvement was seen in symptoms, medication and total scores 1 year after IT had finished, but neither of these showed any significant changes during the follow-up period (Fig. 2). In the 20-CE group the similar scores were very low at the end of IT and further improvement would therefore hardly be registered. The differences between groups in 1980, 1981 and 1986 were not statistically significant when drop-outs in the present follow-up study were excluded.

When no adjustment was made for the approximately 4-fold increase in pollen exposure during the study period, symptom scores increased significantly in the 20-CE group from 0.3/day to 2.0/day (quartiles: 0.0–1.6/day and 0.0–6.3/day). In the 2-CE group median symptoms scores were 3.6/day (1.7–5.7) in 1986 compared to 1.8/day (0.6–3.4) in 1980, this change being of no statistical significance.

Skin prick tests

At the end of and just after IT, skin sensitivity to timothy pollen allergens had decreased significantly. Although the median values reversed from 10 HEP/ml to the initial 1 HEP/ml during

the follow-up period, statistical analysis showed sensitivity to be significantly lower in both groups at the final test compared with the initial test.

Total IgE

Compared with pretreatment values the total IgE in serum was significantly lower in both groups 1 and 6 years after termination of IT (Fig. 3) with median concentrations being 102, 79 and 66 IU/ml in the 2-CE group and 133, 93 and 123 IU/ml in the 20-CE group. The changes seen during the follow-up period were non-significant.

Allergen specific IgE

In the 2-CE group, median allergen specific IgE had decreased during treatment from 18 to 3 SU/ml but at follow-up after 1 and 6 years the antibody levels (9 and 15.5 SU/ml) were not significantly different from pretreatment values (Fig. 4). In the 20-CE group, the antibody levels did not change significantly during the study period, medians being 12, 9, 8 and 16 SU/ml.

DISCUSSION

In the present study the beneficial clinical long-term effect of IT was indicated by a retrospective evaluation and was subsequently verified by medicine and symptom scores during the

Table 1
Grass pollen per m³ collected by regional pollen trap

Year	Total season	Weeks: 24–27
1977	1239	
1978	1365	
1979	1060	
1980	588	277
1981	1667	959
1982	1193	
1983	2638	
1984	1296	
1985	1361	
1986	1284	944

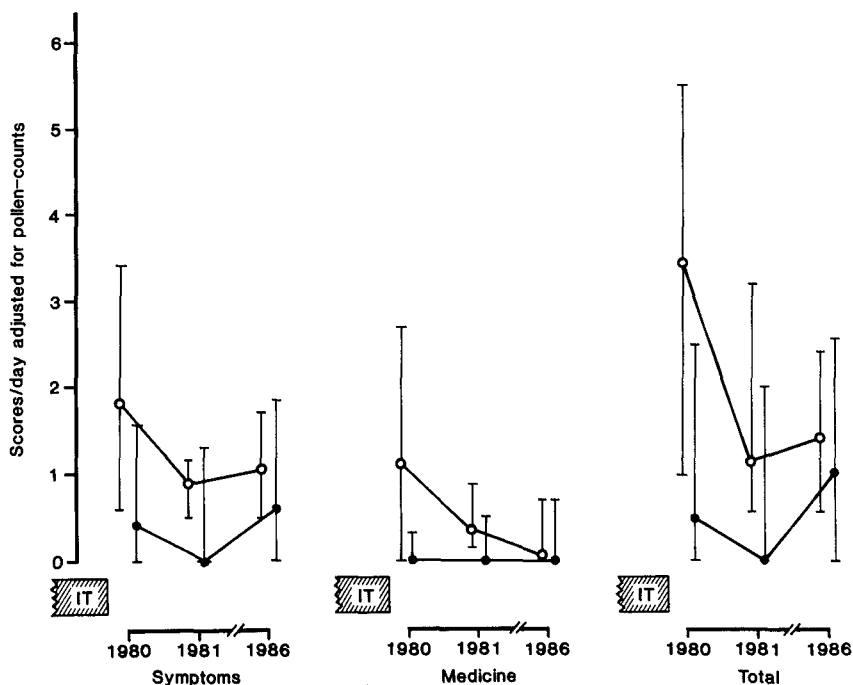


Fig. 2. Daily scores for symptoms, medicine and the sum of these during and following immunotherapy. Adjustment is made for variations in pollen counts (see text). Medians and quartiles are given for 2-CE (○) and 20 CE (●) treated groups.

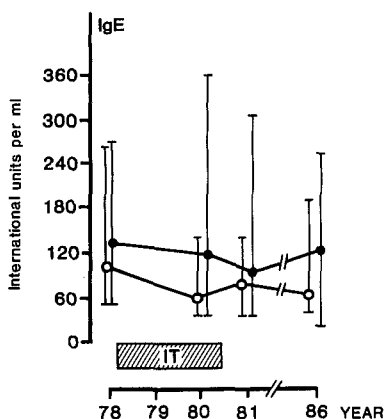


Fig. 3. Serum IgE prior to, during and following immunotherapy. Medians and quartiles are given for 2-CE (○) and 20 CE (●) treated groups.

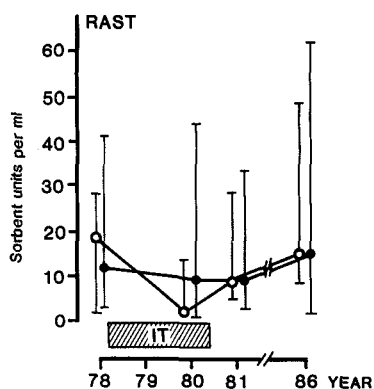


Fig. 4. Timothy-specific IgE prior to, during and following immunotherapy. Medians and quartiles are given for 2-CE (○) and 20 CE (●) treated groups.

pollen season. In contrast, the immunological changes were modest. Since timothy specific IgE was largely unchanged, the small but statistically significant decline in total IgE in serum was probably without any clinical relevance. The findings are in accordance with those obtained during the IT phase of the present study (12, 14).

There are few publications available dealing with the prognosis of hay fever patients not treated by IT. In an early study the spontaneous remission rate was estimated to be 4% p.a. (1). Remission was defined as 2 years or more free of symptoms. In parallel, only one of 13 ragweed hay fever patients reported a (two-fold) reduction in symptoms during a 3-year period (5). In an infant study using less strict criteria, 38% had improved during a 5-year period (9). No control group was included in the present study. It would, however, seem unlikely that the long-lasting therapeutic effect on hay fever reported by 30 of the 32 adult patients in the present study should reflect merely the spontaneous course of the disease.

The treatment period has to be taken into account when evaluating the duration of effect. In house dust mite asthmatics, treatment for 16 weeks would only give 50% relapses within the subsequent 10 months (8), and finishing treatment after 1 year would in 90% of asthmatic children increase the medicine consumption after 1 more year, whereas such increase would be seen in only approximately 30% of those continuing treatment. In contrast, patients receiving IT with insect venom for 5 years were totally protected for at least 1 year (3). Whether treatment for 2½ years, as adhered to in the present study, is optimal has to be elucidated in future studies.

Based on controlled studies on the effectiveness of IT, simple cost-benefit analyses seem to indicate that during treatment the medicine costs would be in favour of IT only in cases with symptoms from several organs and with a prolonged season. An additional drawback of IT is the frequent visits to the physician during treatment. This point is probably the major obstacle for a general acceptance of IT among patients. The nature of the therapy must also be

taken into account. Here the symptomatic and prophylactic medication has the advantage of being unspecific, but the effect does not last when treatment is halted. The duration of the benefits obtained would therefore be a major point when IT and symptomatic treatment are to compete. The indications for IT in hay fever could be extended to include also moderate and less severe cases if a curative, i.e., life-long effect of IT could be proven.

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