

Booster immunotherapy (BIT)

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This study tries to answer two questions: 1) how long does the therapeutic effect of successful immunotherapy (IT) last after termination of the treatment? and 2) what is the best treatment for recidivist patients? To answer the first question, we asked 108 patients with rye/grass pollen allergy who had previously undergone IT for 3–4 years and had responded well to treatment to complete a questionnaire on the course of their recovery after termination of the therapy. Evaluation of the answers revealed a recidivist rate of approximately 30% in the first 3 years. According to our results, the risk of a relapse after this period seems to be low. To answer the second question, we included 40 patients suffering from type I allergy to grass/rye pollen in a clinical study. Each of them had previously undergone specific IT with a grass pollen extract mixture and had terminated this therapy after 3–4 years practically free of symptoms during the grass pollen season. As the symptoms returned and increased from year to year after the end of IT, new therapeutic steps had to be considered. We investigated the efficacy of a short preseasonal injection treatment called “booster immunotherapy” (BIT). BIT was performed with two different injection-regimens, a low-dose schedule comprising six injections and a high-dose schedule with 11 injections, in both cases administered as a build-up regimen. In the next pollen season, 28/40 (70%) patients reported strong improvement or even complete remission of the allergy symptoms. All patients showed a distinct change in their response to provocation tests and in IgG4 antibody titers; however, no correlation between improved *in vivo* or *in vitro* tests and effectiveness of the therapy could be observed. The results show the efficacy of both booster schedules, and we therefore recommend BIT as a valid alternative to repeating conventional, long-term IT.

Immunotherapy (IT) is an approved method of treatment of type I allergic diseases. Much research has been conducted in an attempt to understand how specific IT functions and to determine the resulting clinical benefit (2, 4, 5, 16, 22–25). However, the mechanisms leading to improvement in allergy symptoms remain unknown. In Hymenoptera venom allergy, therapy success correlates well with the rise in specific IgG antibodies (11, 15, 20), suggesting that these antibodies bind to the allergen before it comes into contact with IgE bound to the mast cells in the shock organ. The same rise in IgG and, in particular, IgG4 was also found during IT with pollen or mite extracts (1, 3, 5–7, 10, 17, 21), but here the treatment outcome seems to depend not on the production of blocking antibodies, but on as yet unknown mechanisms (3). In addition to this, little information is available on: 1) how long the therapeutic effect of IT lasts (13, 14, 18), and 2) what the best treatment of recidivist patients is.

In this study, we investigated patients who had

completed a 3-year specific hyposensitization treatment with a mixture of grass pollen extracts and had shown significant improvement in allergy symptoms. We evaluated the recidivist rate in our allergy clinic; moreover, recidivist patients were preseasonally treated by two different short booster immunotherapy (BIT) schedules. The efficacy of BIT was subsequently observed through the following pollen season.

Material and methods

Questionnaire

A total of 108 patients with grass/rye allergy – 52 women and 56 men – participated in this study. The mean age of the subjects was 30.7 years. Most of the patients suffered from seasonal rhinitis/rhinoconjunctivitis (87/108, 80.6%); 21/108 (19.4%) patients also experienced symptoms in the lower respiratory tract (bronchial asthma and/or allergic bronchitis) during the grass pollen season. Grass/rye

pollen allergy was the only clinically manifest sensitization in the patients. Therefore, every subject had previously undergone hyposensitization for 3 years (allergen extracts obtained from ALK, Horsholm, Denmark; Hollister-Stier, Washington, DC, USA). The maintenance dose (equivalent to 60 000 SQ Units/month) was administered monthly with a 70% dose reduction during the pollen season. The patients showed great improvement in their condition after 3 years of injection therapy with a mixture of extracts from different grass pollens; that is, only responders to IT were investigated. The patients were encouraged to report on the course of their allergy in the 3 years after successful IT. The questionnaires included questions concerning whether or not patients had received all scheduled IT injections, patients' personal evaluation of therapy success, and the course of the disease after termination of the treatment (symptoms during the pollen season and need of medication). The results were evaluated by symptom and medication scores.

BIT patients

Forty patients suffering from type I allergy to grass/rye pollen, as proved by case history, skin prick test (SPT), and elevated specific IgE antibody levels for *Phleum pratense*, participated in this study. Each of them had previously been treated successfully with specific IT. They had all noticed increasing symptoms from year to year, and had therefore decided to revisit the allergy clinic 3–4 years after termination of the first treatment. At this time, all patients suffered from seasonal rhinoconjunctivitis, and 10 patients had displayed symptoms of the lower airways (bronchitis/bronchial asthma) at least once during the past grass pollen season. The allergic symptoms were in all cases due to monosensitization to grass/rye pollen allergens. Patients were randomly divided into two groups to compare two different BIT schedules. Group I comprised nine women and 15 men (mean age 32 years); group II nine women and seven men (mean age 29 years). A group of 16 grass/rye pollen-allergic patients who showed the same recurrence of symptoms but who had decided not to start yet with a new injection cycle was used as control group.

Test procedures and antibody evaluations

Blood was collected before starting BIT, after the last injection, and again after the pollen season. Sera were investigated for total IgE, specific IgE, and specific IgG4 for *Phleum pratense* (ALK SQ standardized allergen; Horsholm, Denmark). IgE measurements were taken by the "Magic Lite" method (measuring range for *Phleum pratense*-specific IgE:

1.43–800 SU/ml; ALK); specific IgG4 was evaluated in an LIA assay using an acridinium ester labeled anti-IgG4 antibody (ALK). The results were expressed as percentage of total activity, and they represent the determination of full extracts of *Phleum pratense*. In addition, on these occasions, we performed a conjunctival provocation test (CPT; eye-drops obtained from ALK), following the guidelines described (8), and SPT (9) using the specific allergen (*Phleum pratense*, Soluprick, ALK) plus histamine positive control and saline negative control on four different areas of the volar side of the forearms in one test. Ocular threshold concentration and the size of the SPT lesions were documented. Calculation of mean wheal sizes was performed as described (9). All tests were performed and analyzed by the same person. During the pollen season, the patients were asked to record daily their symptoms and the medication needed in a symptom-score calendar. The only drugs the patients were allowed were non-sedating H₁-blockers and vasoconstrictive eye-drops. These protocols were collected at control 3 (post-seasonal) and evaluated by examining agreement of symptom peaks and medication amounts with the pollen counts on the respective day, and comparing the results of BIT-treated patients with those obtained from the control group.

Injection schedules

The patient group I, high-dose schedule comprised 11 injections at weekly intervals (concentration rising from 200 SQU to 60 000 SQU); 24 patients were treated according to this schedule. The patient group II, low-dose schedule comprised six injections at 14-day intervals from 50 SQU to 10 000 SQU; 16 patients were treated according to this schedule.

BIT was performed with aluminum hydroxide linked vaccines (Alutard SQ, ALK). The treatment started in November/December and ended in April at the latest (flowering period for grass and rye in Austria: May/June).

Results

Questionnaires

The evaluation of the returned questionnaires showed in 105/108 patients no change in their good post-IT condition after 1 year; worsening of the allergy occurred in only three (2.7%; 95% confidence intervals (CI): 0.6–7.95) cases. In year 2 after termination of IT, 90/108 (83.3%) of the patients described their state as markedly improved over that before IT; 18 patients (16.7%; 95% CI: 9.7–26.7) registered an increase – 14 slight, four considerable – in pollinosis symptoms. This trend continued in year 3 after IT: 33/108 patients (30.6%; 95% CI: 22.1–39.9) ob-

served an increase (26 slight, 7 considerable) of their symptoms during the pollen season, and 75/108 (69.4%) reported a continuing therapy success.

In 67/108 patients, IT had already ended 4 years before; in these cases, we could also provide information about the persistence/recidivism ratio after this time period: 45/67 patients (67.2%) described their state as still very good, indicating no change in the recidivist rate (32.8%; 95% CI: 21.9–45.4) after this time period. A control examination of these 45 patients 1 year later (year 5) supported our view that 3 years after successful IT the chance of suffering recidivism is negligible. Data of the questionnaire evaluation are summarized in Fig. 1.

The subjective data supplied by our patients correlated well with the information they gave about their use of antiallergic drugs. Of the patients, 50/108 reported that 2 years after IT no medication at all had been necessary during the pollen season, while 42 needed medication only sporadically, mostly local therapy.

With respect to the relationship between sex and recidivism, 3 years after termination of successful IT a recurrence of the pollinosis was reported by 39% of the female and 23% of the male patients.

BIT

According to case history verified by the respective symptom- and medication-score calendars, 17/24 (70.8%) patients of group I (high-dose group) and 11/16 (68.8%) patients of group II (low-dose group) could be classified as responders to the therapy. These patients were practically free of allergic reactions during the following pollen season. Of the remaining patients, 5/12 showed an improvement in symptoms over previous years, but the success rate was not as striking as in responders. Therefore, it was decided to continue IT for another year. In 7/12 cases, the injections showed no or little effect (non-responders). These patients were encouraged to re-

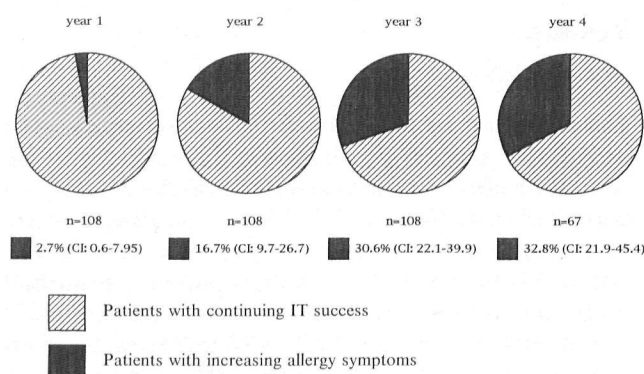


Fig. 1. Recidivist rate in first 4 years after successful hyposensitization in grass/rye pollen allergy.

start IT with our conventional schedule. Other sensitizations responsible for the failure of BIT can be excluded. No correlation between severity of symptoms before BIT and therapy success could be detected.

Antibody evaluations

Specific IgE. *Phleum pratense*-specific IgE of the 40 patients before BIT ranged from 5–>800 SU/ml (mean for group I: 258.8; group II: 219.3) and remained 5–>800 (mean group I: 252.2; group II: 195.8) after BIT. The postseasonal mean IgE level of group I was 250.9; the mean of group II was 213.4. For calculation of the mean values, only IgE levels below the saturation threshold (800 SU/ml) were considered. In neither of the two groups did total IgE show any significant changes induced by BIT.

IgG4. The IgG4 titers increased in all patients after termination of the injection treatment. The increase of IgG4 could not be correlated with the outcome of the therapy. In the postseasonal serum sample, IgG4 had decreased, but in all cases remained still higher than in sample 1 (before IT). Again, no correlation between responders to the therapy and changes in specific IgG4 levels could be observed (Fig. 2).

In vivo tests

SPT. After BIT, reactivity in SPT was reduced in every patient. Mean values of wheal surface reduction were 46.1% for group I, and 30% for group II. There was no detectable difference between responders to BIT and nonresponders. On the third test occasion (after the pollen season), the surface reduction, as compared with the first test, was a mean of 24.5% for group I, and 22.5% for group II.

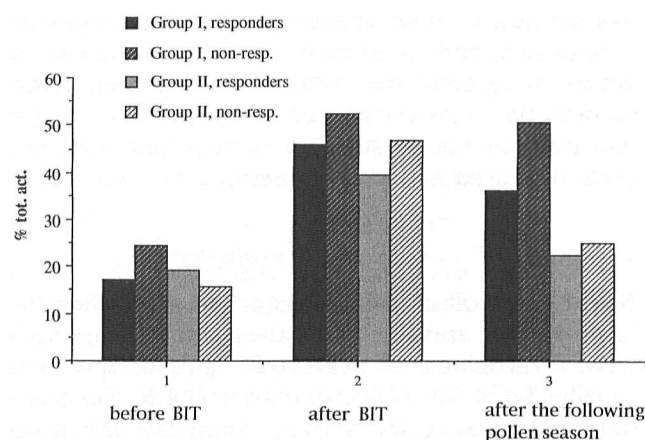


Fig. 2. BIT-induced changes in *Phleum pratense*-specific IgG4 levels.

CPT. CPT revealed a mean dose of 7400 U in group I and 4300 U in group II to induce an allergic reaction in our patients. Post-BIT the provocation threshold was raised to 40 600 U (mean) for group I and to 23 414 U for group II, and it fell again to 23 425/4075 U after the pollen season. In CPT also no significant differences between responders and nonresponders could be detected.

Symptom scores

Analysis of the symptom-score and medication calendars. The symptom peaks of our patients corresponded with the measured pollen concentrations for the respective days in the grass flowering period. Patients of the control group (not BIT-treated) reported symptoms of greater severity and frequency. Moreover, the medication intake was significantly higher in the control group.

Discussion

Immunotherapy is the best treatment in severe cases of type I allergy caused by airborne allergens such as pollen or those of house-dust mite. The efficacy of this treatment has been proved by several clinical studies (2, 12, 16, 22–25). However, few published investigations have focused on the duration of the success of this therapy and thus revealed the recidivist rate (13, 18, 19). Moreover, the available results and opinions vary greatly (18, 19). In our clinic we frequently see patients who exhibit a recurrence of typical hay fever symptoms some years after the termination of hyposensitization. This study tries to elucidate the clinical development of patients successfully treated by IT (thus revealing the recidivist rate), and subsequently to develop an adequate treatment strategy for these cases.

The presented data indicate that approximately one-third (30.6%) of grass/rye-pollen-allergic patients report a distinct relapse in their condition within the first 3 years after termination of successful IT. This percentage stayed constant in the fourth and fifth seasons after IT, providing evidence that patients who are still free of symptoms 3 years after IT run only a low risk of suffering a later relapse.

As IT represents strong immunization (1, 3, 6, 7, 10, 11, 15, 17, 20, 21), we consequently attempted to reactivate curative mechanisms in our recidivist group by boosting. In this study, 40 patients, revisiting our allergy clinic 4–5 years after successful hyposensitization with grass/rye pollen extracts, were preseasonally treated by BIT. The patients were randomly divided into two groups, and treated with two different BIT regimens. A “high-dose schedule” comprising 11 injections and a “low-dose schedule” (six injections) were used.

The clinical evaluation, based on symptom score and medication calendars, showed a success for BIT of 70.8% in the high-dose group, and 68.8% success in the low-dose schedule group. Recidivist patients who did not receive BIT (control group) showed significantly more allergy symptoms, leading to a higher intake of symptomatic antiallergic drugs. A distinct rise of IgG4 levels was observed in all BIT-treated patients, regardless of which injection schedule was applied. However, there was no indication that this antibody rise was connected with clinical outcome of BIT (3, 10, 17). The IgG4 rise seems to be even more pronounced in nonresponders to BIT (Fig. 2), contradicting the disputed theory on the blocking function of this immunoglobulin subclass. IgG4 levels and changes in provocation thresholds seemed to be more consistent in the high-dose-treated group, suggesting that this schedule elicits a longer duration of tolerance; however, the *in vivo* results cannot explain the clinical success or failure of BIT either.

From these clinical results, we conclude that there are memory systems which can be reactivated by boosting with injections of specific allergen. Therefore, BIT could represent a feasible alternative to repetition of long-lasting conventional IT. The immunologic markers for this boosting seem to be more pronounced with a high-dose schedule; therefore, we advise the treatment of recidivist patients by a regimen similar to the build-up schedule of conventional IT – but without progression to the maintenance doses. In our opinion, such a procedure will provide a good clinical effect in most of these patients. Long-term effects of BIT will have to be investigated to determine the duration of this treatment.

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