

**CLINICAL EFFECTS OF SPECIFIC IMMUNOTHERAPY:
A TWO-YEAR DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY
WITH A ONE YEAR FOLLOW-UP**

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Abstract: **Background:** A new depot allergoid of house dust mite (*Dermaphagoides pteronyssinus* – D.pt) has been created in line with the principles and methodology established in the successful development of pollen allergoids. A two-year double-blind placebo-controlled clinical trial, with one further follow-up year of active treatment, has been conducted to assess clinical efficacy and tolerance.

Methods: 40 patients (20 verum and 20 placebo) with IgE-mediated mite allergy and a history of moderate to severe perennial symptoms of rhinoconjunctivitis with or without asthma participated in a 2-year randomized, double-blind, placebo-controlled trial. Actively treated patients were included in a follow-up year. Active treatment was performed with an aluminium hydroxide adsorbed house dust mite allergoid. Parameters for baseline data and clinical efficacy: nasal challenge, quantitative skin prick testing, Visual Analog Scale (VAS), patients' diaries, physician's assessment of patients' health condition, symptoms and use of anti-allergic medication as well as adverse reactions and changes in specific IgG₄ and IgE antibodies.

Results: The trial detected superiority ($p < 0.05$) of mite depot allergoid versus placebo with regard to VAS and symptom intensity sum score in patients who needed anti-allergic medication in the baseline period. Significant differences ($p < 0.05$) between verum and placebo groups were also seen for patients' reactivities to nasal challenges and prick tests with allergen. The blinded assessment by the physician documen-

ted a significant difference ($p < 0.05$) between the groups in favour of active treatment. After reaching the maximum dose as well as after 12 and 24 months, specific IgG₄ antibody concentrations were significantly elevated in the verum group ($p < 0.05$) by comparison with placebo. Local reactions were less frequent in the verum group and no systemic adverse reactions occurred. A third year of active treatment resulted in further improvement and documented the advantage of booster therapy to stabilize the clinical success.

Conclusion: Specific immunotherapy with a mite depot allergoid induced significant clinical improvements versus placebo. Safety was assessed as excellent, and no systemic adverse reactions occurred.

Key words: allergen specific immunotherapy, allergic rhinoconjunctivitis, allergoid, clinical efficacy, house dust mite.

Introduction

IgE-mediated perennial allergy with symptoms such as rhinitis, conjunctivitis and/or asthma is very frequently caused by grass and tree pollens and also by house dust mites [1]. After the establishment of a specific diagnosis by an experienced allergologist using well characterized extracts, the patient may be well advised to undergo specific immunotherapy to alleviate his allergic symptoms of rhinitis, etc. Allergen avoidance, which is particularly difficult with perennial house dust mites, and immunotherapy represent the only causal treatments that can be offered to the allergic patient. Otherwise various anti-symptomatic treatments are available, but in spite of the introduction of even more efficacious and potent drugs, both the morbidity and the mortality of asthma are increasing. Furthermore, immunotherapy is also expected to diminish the risk of a progression from rhinitis to asthma, and thus positively influence morbidity and mortality. [2, 3, 4].

Extensive research has been invested to make immunotherapy more effective and safer as well as to increase the compliance of the patients. Allergoids are considered very useful in this respect [4, 5]. They are prepared by chemical modification of purified native allergen extracts. The modification causes a very substantial reduction of allergenicity of the extract as can be judged by skin testing, histamine release from sensitized leucocytes and measurement of specific IgE-binding activity by RAST-inhibition [6]. However, immunogenic activity and T-cell reactivity are retained [7, 8].

These properties enable the allergoids to be used as a basis for allergen specific immunotherapy with a reduced risk of inducing IgE-mediated reactions; it has become possible to achieve high doses of immunogen over shorter time courses than is possible with native allergens. Clinical studies have shown good tolerance of aqueous pollen allergoids by comparison with allergen pre-

parations (9, 10). Adsorption of pollen allergoids onto aluminium hydroxide suspensions resulted in depot preparations which have been investigated in a series of clinical studies and shown to be well tolerated and to have good clinical efficacy [11, 12, 13, 14, 15, 16, 17, 18].

The principles and methodology established in the development of pollen allergoids have now been adapted and extended in creating a new house dust mite allergoid with *Dermatophagoides pteronyssinus* (D.pt.) in a depot formulation with aluminium hydroxide. In order to assess efficacy and safety of this preparation, a two-year double-blind placebo-controlled trial was performed and results of this study with a one year follow-up of active treatment are now available and presented here.

Material and methods

Patients

Planned number of subjects at this centre: 40 patients (20 active and 20 placebo); enrolled: N = 40; analyzed: N = 40. Only actively treated patients (n = 20) participated in an active follow-up year.

For the inclusion all patients had to be diagnosed with IgE-mediated allergy and a positive history of moderate to severe perennial allergic rhinoconjunctivitis and/or asthma, attributable to house dust mites *Dermatophagoides pteronyssinus* (D.pt.), with a positive provocation test result and score values between 4 and 10 on the VAS. Main exclusion criteria were: clinically relevant allergy to other perennial allergens or to pollens; severe asthmatic symptoms, FEV₁ < 70% of the theoretical value.

Study design

A 2 year double-blind, placebo-controlled treatment was performed perennially at the trial centre in Skopje, Macedonia. Patients who met all selection criteria were assigned a patient number according to sequence of inclusion in the treatment phase and received the appropriately numbered preparation. The assignment of numbers to treatment groups was based on a computer-generated randomization list. Following evaluation of the data from this placebo-controlled phase, a third treatment year was added for the actively treated patients without interruption of the perennial hyposensitization.

Procedure

The study was performed in accordance with the Declaration of Helsinki (1964 and revised versions up to 1996), the GCP and ICH and was approved by the responsible ethics committee of the Medical Faculty of Skopje University. The patients were carefully informed of aims, risks, duration and

insurance of the trial and gave their written consent. At inclusion, patients' baseline values were assessed regarding skin reactivity, nasal challenge reactivity, VAS and results from patients' diaries as well as immunological parameters including allergen specific IgE and IgG₄ antibodies. For the assessment of treatment efficacy, the investigations were repeated at the end of each trial year and supplemented by the physician's assessment in changes the patients' health condition, symptoms and anti-allergic medication. Additional serum examinations were performed after the maximum dose was reached; patients' diaries were completed every fourth month for four weeks each (Fig. 1).

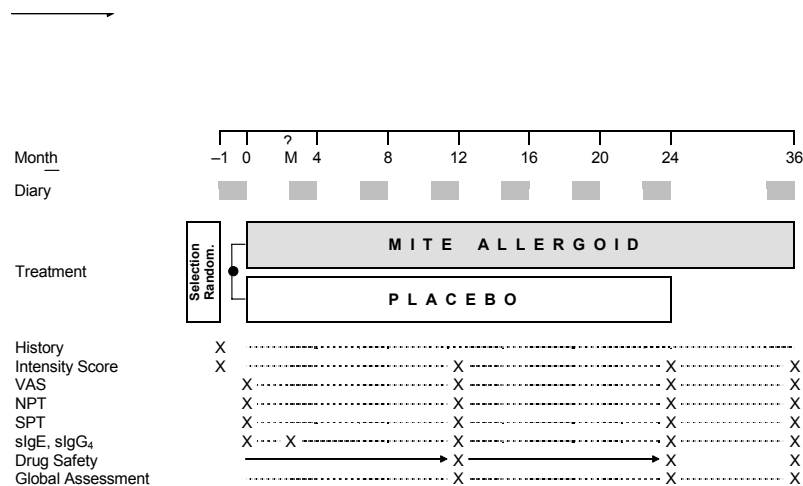


Figure 1 – Flow Chart (M = 2 weeks after reaching the maximum dose)

Слика 1 – Дизајн на студијата (M = 2 недели по достигнувањето на максималната доза од имуноterapiјата)

During the trial, anti-symptomatic medication was allowed as needed and had to be documented; for reasons of better comparability, the physician recommended similar / the same drugs for all patients if possible and with respect to baseline data. The trial medication was injected subcutaneously at weekly intervals during the initial treatment period and at 4–6 week intervals during the perennial maintenance treatment. In line with the conventional approach, a third year of immunotherapy was added for the actively treated patients only.

Assessment of clinical parameters

Baseline data and changes in health condition during the treatment course (after 12 and 24 months) were assessed with the following methods.

Nasal provocation test: Individual threshold concentrations of *D. pt.* allergen inducing a positive nasal provocation response were compared at different dates. A rhinomanometer was used to measure nasal flow and resistance values.

Prick tests: Blinded randomized use of quantitative prick testing on different occasions with five threefold concentrations of glycerinated solutions of *D. pt.* allergen together with histamine dihydrochloride references 0.1% and 1% to compare histamine related weal areas after 15 minutes.

For all quantitative tests, appropriate avoidance of anti-symptomatic drugs was required and lyophilized allergen and solvent for reconstitution / dilutions were supplied from identical batches to secure comparability of results at different dates.

Visual Analog Scale (VAS): Individual patient's subjective assessment of health condition recorded on the VAS (scores: 1 to 10 points with 1 point = good; 10 points = poor) was considered as primary endpoint.

Physician's registration of patient's symptoms: At the above-mentioned dates individual clinical symptoms were assessed with regard to organ (nose, eyes, lungs) and type of symptom (e.g. nose: itching / sneezing / rhinorrhea / blocked nose), intensity of complaint (mild, moderate, severe) and frequency (sporadic, 2–3x per week, daily).

The rank sum of changes in VAS and the intensity sum score were analyzed as a multiple endpoint according to O'Brien's nonparametric procedure.

Physician's assessment of changes in patients' condition: The assessment was made in terms of "patient improved considerably / improved / did not change / deteriorated".

Patients' diaries: Allergic symptoms and anti-symptomatic medication were recorded by the patients in standardized diaries every fourth month over a 4-week period and during a baseline period before the start of the treatment. Scores were calculated from the information that had to be given daily during the requested months on symptoms with regard to organ (nose, eyes, lungs), type of symptom (e.g. nose: sneezing / rhinorrhea / blocked nose), intensity of complaint (1–3, i.e. mild, moderate, severe) and anti-symptomatic medication with trade name and dose taken.

Safety: All adverse events and adverse drug reactions were documented and assessed. Numbers of local and systemic adverse reactions with causal relationship to the injection were counted and compared between the groups.

Assessment of specific antibody responses

Specific human IgE antibodies were measured using the Allervance system (Allergopharma, Reinbek, Germany) with *D.pt.* allergen discs according

to the manufacturer. Values were determined as kUa/l and the detection limit of 0.35 kUa/l. *D.pt.* allergen extract coated wells were incubated with serum samples, diluted at least 1: 2. Therefore, the limit of detection was 8 µg/l.

Bound human IgG₄ antibodies were detected by using the monoclonal biotinylated anti-human IgG₄ antibody G17-4 (BD Biosciences; 1 µg/ml) and alkaline phosphatase labelled streptavidin (Sigma S 2890; 1 µg/ml) with pNPP as substrate. Reference microtitreplate wells were coated with anti-human IgG₄ antibody JDC-14 (BD Biosciences; 2 µg/ml) and subsequently incubated with purified human IgG₄ (Sigma I 4639) as reference, with concentrations of 2000 µg/l to 4 µg/l. Plates were read at 405 nm after 15 min substrate incubation.

Trial preparations

Active treatment was performed with an aluminium hydroxide adsorbed house dust mite *D.pt.* allergoid. (House dust mite allergens are extracted from purified mite bodies of *Dermatophagoides pteronyssinus* with buffered saline, partially purified by diafiltration, characterized, chemically modified by treatment with aldehydes and adsorbed onto aluminium hydroxide.) Concentrations of the active trial preparations were 300 PNU/ml (strength A at the start of treatment) and 3,000 PNU/ml (strength B for maintenance treatment). Physiological saline served as the placebo solution and contained caramel as a colouring agent and histamine dihydrochloride (for blinded tolerance examination). The dosage schedule for the double-blind treatment mentioned volumes. All trial preparations were supplied by Allergopharma. Packing material was uniform in design; each package was marked as trial medication.

Immunotherapy

The double-blind s.c. injection of the trial medication was performed at (1–2) weekly intervals provided that the previous dose was well tolerated; dose modifications were stated. Dosage guideline: strength A (ml) 0.1; 0.2; 0.4; 0.6; strength B (ml) 0.1; 0.2; 0.4; 0.6. The maximum dose stated was not to be exceeded and maintenance treatment with the maximum dose could be performed with intervals of 4 weeks up to 8 weeks. After an injection the patient had to be kept under close supervision for at least 30 minutes and the patient's condition had to be assessed before he/she left the clinic. Dosage modifications: After local reactions with a diameter of 5–10 cm, the dose had to be repeated; with a diameter of >10 cm, the last well tolerated dose had to be repeated. After a mild systemic reaction, the dose was to be reduced by 2–3 steps; after a severe systemic reaction, therapy was to be reinitiated with strength A or discontinued.

Statistics

Changes from baseline after 12 and 24 months of treatment in patients' VAS entries and in the intensity sum score as assessed by the investigator were analyzed as a 'global' efficacy measure according to O'Brien [19, 20]. Inter-group tests were carried out nonparametrically (Mann-Whitney's U test) or by means of ANOVA with a need of anti-allergic medication in the baseline period as cofactor. Repeated measurements of continuous variables were compared by means of ANCOVA using baseline values as covariate, and χ^2 test was used for categorical data. Test results $p < 0.05$ were considered as statistically significant.

The sample size of this study was determined prospectively based on a standardized treatment difference of approx. 0.9 observed in a similar study with grass pollen allergoids. The minimum number of 56 completers was planned to be realized in two centres with 40 patients each. Unexpected delays in patient recruitment in the second centre resulted in a lack of synchronization in respect of the immunotherapy and time of maximum exposition between the centres. Therefore, the results of the trial centre in Skopje, Macedonia, which performed the study under homogeneous study conditions were analyzed and reported separately.

Results

Patients

40 patients had been planned and enrolled at the trial centre. None of the patients had had immunotherapy treatment before. There were no drop-outs and all 40 patients (20 verum; 20 placebo) completed the study treatment and testing according to the protocol and were included in the final analysis (Table 1).

Table 1 – Табела 1

Baseline Characteristics

Вредносии на испишуваниие параметри пред почейокоий на итераијата

| Randomized treatment group | | Active [N=20] | Placebo [N=20] |
|-----------------------------------|-----------------|---------------|----------------|
| Age [years] | median (range) | 27 (18 – 57) | 33 (18 – 62) |
| Sex | female / male | 5 / 15 | 10 / 10 |
| Symptoms during last 3 months | • eye symptoms | 4 | 4 |
| | • nose symptoms | 20 | 20 |
| | • lung symptoms | 11 | 9 |
| Duration of nose symptoms [years] | median (range) | 5 (2 – 13) | 9 (1 – 42) |
| Asthma bronchiale | | 11 | 6 |

| | | | |
|--|---------------------|--------------|--------------|
| RAST / CAP D. pteronyssinus | median (range) | 3.0 (2 – 6) | 3.5 (2 – 6) |
| Interval scale | median (range) | 6.0 (5 – 8) | 6.0 (5 – 8) |
| NPT threshold dose [SBE/mL] | 500 1500 5000 | 18 2 – | 12 6 2 |
| Skin test reactivity [Average SI relative to histamine 1.0%] | mean ± SEM | 0.46 ± 0.06 | 0.42 ± 0.07 |

Immunotherapy

All 40 patients tolerated the dosage schedule and the maximum dose as stated in the protocol and all patients also participated in the maintenance treatment until the end of the trial. During the initial treatment an average of 8 injections were given to reach the maximum dose which had then been repeated during maintenance therapy (approximately 20 further injections) until the end of the double-blind investigation. A further 10 to 12 injections were given to each of the actively treated patients during the additional third trial year.

Safety assessment

The incidence of local reactions following verum injections was markedly lower than with placebo injections (containing histamine-dihydrochloride for blinding reasons). Local reactions with a diameter of less than 5 cm at a maximum were seen after 4.6% of the active injections and 17.4% following placebo injections. Larger local reactions with a diameter of at least 5 cm were seen in 1 actively treated patient and in 3 placebo patients. Systemic allergic reactions were not observed.

Adverse events were documented in 7 actively treated and 8 placebo-treated patients (9 and 11 symptoms, resp.): 4 actively treated and 6 placebo patients had infections; 1 actively treated and 3 placebo patients had a headache; 2 actively treated patients and 1 placebo patient had a cough; for 1 placebo-treated patient a skin burn on the foot was reported.

Clinical efficacy

All 40 patients fulfilled the inclusion criteria of positive test results from nasal provocation tests and prick tests with mite D.pt. allergen. These individual test results were taken as baseline values for comparison and showed the following changes during the trial.

Evaluation of data from nasal challenges showed a statistically significant improvement after 24 months of active treatment as compared with the placebo group (U test of threshold doses: $p < 0.05$). After only 12 months, there

was already a slight, though not significant, trend towards this change of nasal reactivity. After 36 months of active treatment, the challenge tests resulted in a negative test result for 19 of the 20 patients.

Quantitative prick test showed a significant reduction of skin reactivity after 12 ($p < 0.01$) and 24 ($p < 0.001$) months of treatment in favour of the actively treated group in comparison to placebo. The average AUC of the weal areas following 5 doses of mite allergen, related to a 1% histamine dihydrochloride reference solution, decreased from 0.46 ± 0.27 over 0.22 ± 0.22 to 0.24 ± 0.24 with mite allergoid, but increased from 0.46 ± 0.32 over 0.39 ± 0.37 to 0.54 ± 0.47 with placebo.

Physician's assessment

Significant changes ($p < 0.05$) were found between the two trial groups after 12 and 24 months of treatment regarding the patients' condition as assessed by the physician (Table 2). For 90% of the actively treated patients an 'improved/considerably improved' condition was documented during the two double-blind trial years. The differences versus placebo ranged from 25 to 40%; a deterioration was only seen in the placebo group.

Table 2 – Табела 2

Physician's Assessment of Patients' Condition

Лекарска процена на здравствената состојба на пациентите

| Assessment | Active | | | Placebo | |
|-----------------------|----------|----------|----------|----------|----------|
| | 1 year | 2 years | 3 years | 1 year | 2 years |
| Considerably improved | – | 5 (25%) | 15 (75%) | 1 (5%) | 2 (10%) |
| Improved | 18 (90%) | 13 (65%) | 5 (25%) | 9 (45%) | 11 (55%) |
| Not changed | 2 (10%) | 2 (10%) | – | 10 (50%) | 6 (30%) |
| Deteriorated | – | – | – | – | 1 (5%) |

After a total of three years of active treatment, all [20] patients had considerably improved (75%) or improved (25%).

Physician's assessment of patient's condition was partly based on the intensity sum score which showed marked but not significant differences in favour of active treatment when analyzed as a single endpoint (further details see below).

Patients' records

The VAS showed an improvement in both trial groups with a clear but not statistically significant difference in favour of active treatment when analyzed as a single endpoint (further details see below).

Within the actively treated group, the median score on the VAS improved by 3 points from a baseline value of 6 to a score of 3 after 12 and 24 months. A further improvement to a median of 2 on the VAS was documented at the end of three years immunotherapy. This obviously represented a statistically significant intragroup change from baseline ($p < 0.001$) but firstly a highly relevant clinical result because all patients improved by at least 3 points (to 6 points) on the VAS.

By means of patients diaries, a reduction of the anti-symptomatic drugs needed by the patients mainly for bronchial disorders was seen at the end of the first trial year. At the end of the second trial year, a significant ($p < 0.05$) difference between the groups was documented for the need of anti-symptomatic medication in favour of the actively treated patients (Figure 2). In respect to the symptom score derived from patients' diaries, no statistically significant treatment differences were detected.

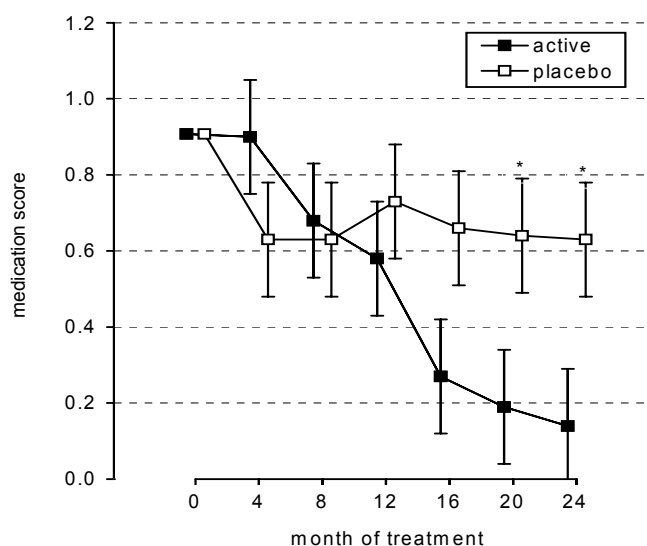


Figure 2 – Baseline Adjusted Means \pm SEM of Medication Score from Patients' Diaries (*: $p < 0.05$)

Слика 2 – Средна вреднос̄и \pm SEM од њојребајиа за лекови адајѣиранайиа за базалније вреднос̄и (*: $p < 0,05$)

Combined analysis of VAS and intensity sum score:

Using the ranks of changes from baseline in the VAS and the intensity sum score after 12 and 24 months of treatment as a 4-item multiple endpoint, the mean rank sums worked out at 96.2 ± 10.9 (mean \pm SEM; active) and 93.3 ± 8.7 (placebo) in patients without need of anti-symptomatic medication in the baseline period. The treatment difference was obviously insignificant.

But in patients with symptomatic medication in the baseline period indicating a more severe condition of the mite allergy, statistically significant differences between the mean rank sums of 52.0 ± 9.8 (active) and 89.3 ± 13.3 (placebo) were obtained ($p < 0.05$; higher improvement with active treatment).

Changes of immunological parameters

Specific IgE antibodies against D.pt.: Two weeks after the individual maximum doses had been reached, no significant changes from baseline values were seen and also, during the course of the treatment, sIgE did not change significantly in either group.

Specific IgG₄ antibodies against D.pt.: Evaluation showed significant differences between the groups for serum samples taken at the end of the initial treatment ($p < 0.01$) as well as after 12 ($p < 0.001$) and 24 months ($p < 0.001$). Only active treatment produced a significant increase of specific IgG₄ antibodies in patients (Figure 3).

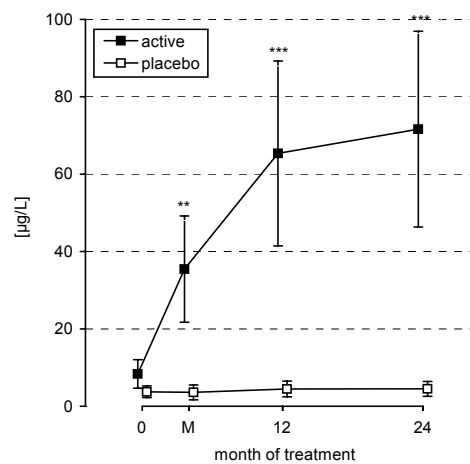


Figure 3 – Means \pm SEM of sIgG₄ (M = 2 weeks after reaching the maximum dose; **: $p < 0.01$; ***: $p < 0.001$)

Слика 3 – Средна вредносћ \pm SEM за sIgG₄ (M = 2 недели по досћигнувањемо на максималнаја доза; **: $p < 0,01$; ***: $p < 0,001$)

Discussion

The new depot allergoid has been produced and now clinically tested to document its usefulness for specific immunotherapy. For the patients included in this study, neither an allergen avoidance nor an exclusive use of anti-symptomatic medication presented an optimal solution for their allergic symptoms caused by house dust mites. Immunotherapy was indicated for these patients, and superiority to placebo was documented for the depot allergoid of mites used in this double-blind investigation.

Positive results of specific nasal challenge tests and prick tests are a prerequisite for the appropriate indication of immunotherapy with a perennial allergen, and the marked reduction of the patients' nasal and skin reactivity documented by the significant difference versus the placebo patients is therefore considered an impressive effect of this form of treatment. The clinical relevance of this favourable reduction of patients' specific reactivity upon the "artificial" allergen exposition may be realized from further clinical results, i.e. from the physician's assessments or from patients' diaries, written during the natural exposition. At the end of the trial, there was a significant ($p < 0.05$) difference between the groups, in favour of the actively treated patients, regarding the reduction of the anti-symptomatic drugs needed by the patients. Regarding symptom scores from the diaries, only a non-significant movement towards improvement was documented. However, physician's assessment on patients' improvement also resulted in a significant difference ($p < 0.05$) between the groups in favour of mite depot allergoid, and the unblinding revealed that 90 % of the actively treated patients had improved.

Results gained by the patients' subjective assessment of their condition by means of a VAS had been considered as primary endpoint but could not document superiority here in terms of significance as was seen in some trials with seasonal allergens. This missing significant result left the question whether it was due to the unintentionally small number of patients included in this trial open. Parameters like symptoms, possibly with more weight on intensity, the need for anti-symptomatic medication and the sensitivity of the allergic organs may be more reliable, as also discussed by other investigators, to assess the stage of disease and to monitor changes during immunotherapy [21, 22]. But the median score on the VAS also improved, and that by 3 points from a baseline value of 6 to a score of 3 after 12 and 24 months of active treatment. Additionally an improvement to a median of 2 on the VAS was documented at the end of three years active treatment, which represents a highly significant change ($p < 0.001$) after immunotherapy.

For more transparency, however, the consideration of patients with symptoms strong enough to induce the need for anti-symptomatic medication seems important. After all, for the VAS and symptoms intensity score this trial

documented a significant superiority of the verum treatment for patients who needed anti-symptomatic medication during the baseline period. In patients without drug consumption no relevant treatment differences were obtained, most likely because of only low levels of complaints.

In line with these results of successful immunotherapy is also the significant difference ($p < 0.05$) between the groups in respect of increases of specific IgG₄ antibodies; the clinical impact of this change is still open, but this increase was only seen in sera of actively treated patients.

The very important aspect of safety of immunotherapy has been documented positively in this trial: The new depot allergoid caused no systemic reactions and local reactions with a diameter of more than 5 cm were seen in only one patient. Thus patients were not much bothered by adverse reactions, and in fact, there were no drop-outs. Safety data also demonstrate the usefulness of the dosage schedule: All patients tolerated the maximum dose of the depot allergoid, and already after about eight weeks – appreciably sooner than with allergen preparations used in conventional immunotherapy – they had reached the start of the maintenance treatment, which offers longer intervals between injections. This fact has most probably also increased the patients' compliance, preventing drop-out and encouraging treatment phases that were long enough to secure efficacy of immunotherapy. This, too, is considered to be of great importance, especially with regard to interference in the progression of the severity of the allergic symptoms and / or the progression from allergic rhinitis to asthma [1, 2, 3, 4].

In line with convention, a third year of immunotherapy was added for the actively treated patients ($n = 20$). This third year of active treatment resulted in further improvement of patients' clinical data documenting the advantage of booster therapy for the stabilization of clinical success.

For a next step further studies may be recommended with larger numbers of patients to monitor more patients. It is also considered important to further investigate the different clinical parameters to find the most predictive one for clinical efficacy of perennial and / or seasonal immunotherapy.

In summary, results from this trial document that immunotherapy with the well characterized new depot allergoid is safe and efficacious provided that it is conducted in a clinical environment that ensures correct diagnosis and performance of immunotherapy.

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Резиме

**КЛИНИЧКИ ЕФЕКТИ НА СПЕЦИФИЧНАТА ИМУНОТЕРАПИЈА:
ДВЕГОДИШНА ДВОЈНА СЛЕПА, ПЛАЦЕБО КОНТРОЛИРАНА
СТУДИЈА СО ДОПОЛНИТЕЛНА ГОДИНА НА FOLLOW-UP****Д. Докиќ¹, Ј. Шниткер², А. Наркус³, О. Кромвел³, Е. Франк³**¹Клиника за пулмологија и алергологија, Р. Македонија²Институт за применета статистика, Германија³Алергофарма Joachim Ganzer KG, Германија

Вовед: Во последниве години е создаден нов депо алергоид составен од домашни микрокрлежи (*Dermatophagoides pteronyssinus*), следејќи ги принципите и методологијата коишто веќе успешно се применуваат во кривањето на поленските алергоиди. Со цел да се процени ефикасноста и толеранцијата на новиот депо алергоид составен од домашни микрокрлежи, се изведе двегодишна, дуplo слепа, плацебо контролирана клиничка студија. Пациентите коишто беа на активен третман (со *vegum*) продолжија да ја примаат терапијата уште една година.

Методи: Во двегодишната, рандомизирана, дуplo слепа, плацебо контролирана студија учествуваа 40 пациенти со докажана ИгЕ – посредувана алергија на домашни микрокрлежи и со анамнеза за средно тешки до тешки симптоми на ринокоњунктивитис. Од нив 20 примаа *vegum*, а 20 пациенти плацебо. Пациентите коишто беа на активен третман (со *vegum*) продолжија да ја примаат терапијата уште една година. Активниот третман се состоеше од алергоид составен од домашни микрокрлежи апсорбиран на алуминиум хидроксид. Следниве параметри беа земени за појдовни во еволуцијата на клиничката ефикасност на специфичната имунотерапија: назалната провокација, квантитативниот прик тест, визуелната аналогна скала (VAS), дневникот на пациентите, лекарската оценка на здравствената состојба на пациентите, симптомите на пациентите, употребата на анти-алергиските лекови, несаканите реакции и промената на специфичните IgG и IgE антители.

Резултати: Клиничката студија покажа супериорност на алергоидот составен од домашни микрокрлежи наспроти третманот ($p < 0,05$). Тоа се однесува на VAS и на интензитетот на симптомите, особено кај пациентите што имале потреба од анти-алергиски лекови пред почетокот на терапијата.

Исто така беше забележана сигнификантна разлика ($p < 0,05$) помеѓу *vegum* групата и плацебо групата во однос на назалната провокација и кожниот прик тест со алергени од домашните микрокрлежи.

Во оваа студија беше забележана сигнификантна разлика ($p < 0,05$) во лекарската проценка (слепа) на здравствената состојба на пациентите по

меѓу активно третираната и плацебо групата. По достигнувањето на максималната доза како и по 12 и 24 месеци од третманот, се детектира сигнификатно покачување на нивото на специфичните IgG4 антитела ($p < 0,05$) кај vegum групата во споредба со плацебо групата. Локалните несакани реакции беа поретки кај vegum групата отколку кај плацебо групата, додека пак, системски несакани реакции не беа забележани.

Третата година со активен третман резултираше со понатамошно подобрување на параметрите. Со тоа се документираше предноста на "booster" терапијата во стабилизирањето на клиничката ефикасност.

Заклучок: Специфичната имунотерапија со депо алергоид составен од домашни микрокрежи индуцираше сигнификантно клиничко подобрување кај vegum групата во споредба со плацебо групата. Сигурноста на ваквата терапија беше оценета како одлична без појава на системски несакани ефекти.

Клучни зборови: алерген специфична имунотерапија, алергиски ринокоњунктивитис, алергоид, клиничка ефикасност, домашни микрокрежи

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