Clinical Effects of Specific Immunotherapy with a new House Dust Mite Allergoid
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Patients and methods

It became into the study 40 patients (in Active and Placebo-groups each 20) included (Tab. 1). Inclusion criteria were an IgE-mediated allergy against house-dust-mites, a positive history of an average up to severe perennial allergic rhinoconjunctivitis with or without asthma through *Dermatophagoides pteronyssinus*, a positive nasal provocation-test [NPT] and troubles equivalent 4-10 Score on the visual analogue-chart (VAS). The main exclusion criteria were clinical relevant allergies against different perennial allergens or pollens, severe asthma-symptoms and forced expiratory volume in 1 second (FEV$_1$) < 70% of the setpoint.

Study-design

Patients, that fulfilled the inclusion criteria, became according to randomisation plan in the sequence of their inclusion into the therapy-phase double blind two-year perennial therapy with active or placebo assigned. According to evaluation of the placebo controlled phase received the patients of the active group toward the completion of the recommended three-year immuno-therapy a third continuation-year, while placebo treated patients based on the still limited data-situation SIT with an established mite-preparation (Novo-Helisen Depot®) was offered.

Study-course

The study became in accordance with the current declaration of Helsinki, the ICH-GCP-guidelines and after affirmative vote of the ethics-commission implemented. The patients gave after thorough explanation their written approval for the study-participation. After inclusion a determination of the exit-values followed of pricktest, NPT, VAS, patient-diary-criteria as well as the allergen specific IgE- and IgG4-antibodies. For the assessment the potency of the therapy became the investigations at the end of an every treatment-year repeated and through a medical assessment the changes of the health-status, the symptoms, the demand for anti-allergic medication as well as serum investigations after reaching of the maintenance-dose completed.

Throughout the clinical trial the use of symptomatic medications on demand were allowed, local alpha- or beta-mimetics, oral/ local antihistamines respectively, local/ oral glucocorticoids were regarded with a corresponding score value in the symptom medications score (SMS). The trial medication (*Dermatophagoides-Pteronyssinus-Depot-Acaroid®*) became during the run in-phase through the interval of 7 (up to 14) days, while the perennial continuation-treatment every 4 (up to 8) weeks subcutaneously injected.

Clinical parameters

The exit-data as well as the changes of the health condition after 12 and 24 months were assessed with the following methods. For all quantitative allergy-test at the
patient became a corresponding waiting period at the use more symptomatic medication maintain.

NPT: Rhinomanometric determination the threshold-concentration of the *Dermatophagoides-pteronyssinus*-Allergens (500, 1,500, 5,000 SBE/ml) before and during therapy.

Prick test: blinded, randomised, quantitative pricktests with each five triple-concentrations glycerinated solutions of the *Dermatophagoides-pteronyssinus*-allergens, as positive-controls of 0.1% and 1% histamine dihydrochloride solution. The wheal-surface of the allergen tests was assessed after 15 minutes in comparison to the histamine reaction.

VAS: individual assessment of the health condition by the patient on a scale of 1 (good) up to 10 (bad) points. The rank-sum of the changes and the intensity scores didn't become parametric as multiple end points according to O'Brien analyzed (15, 22).

Medical evaluation of the symptoms: The individual symptoms at nose, eye and lung, e.g. itching, itchy nose, running nose and nasal obstruction, were graded by the treating doctor as mild, moderate or severe and that frequency (sporadic, two to three times per week, daily) assessed; furthermore were assessed, by the patient himself - being considerably improved, improved, remained unchanged or made worse.

Patient-diaries: Throughout the baseline-phase as well as all 4 months during the treatment became allergic symptoms (e.g. itching, itchy nose, running nose, congested nose), intensity and the taking of symptomatic medications (trade-name, dose) by the patient over presently 4 weeks in standardized day-books as score point values daily-topical documented. Symptoms were as follows assessed 0, none 1, mild 2, moderate 3, severe. For the daily use of medication became regarded local alpha-or ß-mimetics 1, local/ oral antihistamines 2, local/ oral glucocorticoids 3.

Tolerance: Unwanted events were documented and evaluated as well as the number of more local and systemic reactions, for a causal correlation with the injection-therapy as possible, probable or certain appeared, and compared.

**Determination of specific IgE-and IgG4- antibodies**

Specific IgE-antibody became by means of the all-vance-system (Allergopharma, Reinbek) according to manufacturer's recommendation with *Dermatophagoides-pteronyssinus*-Allergen disk at a verification boundary of 0.35 kUa/l determined. For the determination more specific IgG4- antibodies became with *Dermatophagoides-pteronyssinus*-Allergen extract protein coated microtitre plates [MTP] utilized. As reference became cleansed human IgG4- myeloma (Sigma I-4639) in concentrations of 4-2,000 µg/ml put in, and overall 20 dilutions per MTP (ten concentrations of the reference in double determination became with anti-human IgG4- antibodies (clone of JDC-14, BD Biosciences of 2µg/ml) coated.
Results

Specific immunotherapy

All 40 patients could be treated according to the recommended dosing scheme and reached with average eight injections the appointed maximum-dose. Up to the end of the double blind study-section of 20 further continuation-injections became about applied into the third study-year further of ten up to twelve injections. All patients finished the study for the appropriate test plan.

Tolerance

Local reactions stepped under the treatment with the allergoid clearly more uncommon on as under placebo which contained the blinded Histamine. Local reactions with a diameter < 5cm became at 4.6% the injections with active (placebo 17.4%) observed. Local reactions of ≥ 5cm stepped with one active and with three with placebo patients treated. Systemic allergic reactions were not observed.

Unwanted events were with seven active and eight with placebo patients treated documented (presently nine and eleven events): four active and six with placebo treated patients had infections; an active treated patient and three patients of the placebo group suffered headaches; two actively treated patients and one with placebo treated patient complained about cough; a patient in the placebo group reported about stinging skin on the foot.

Clinical efficacy

All 40 patients demonstrated at study-commencement reactivity to the mite (Dermatophagoides-pteronyssinus) allergen through the nasal provocation as well as in the prick test. After 24-months treatment under Acaroid®-therapy a statistically significant improvement in the NPT in comparison to placebo could be demonstrated (5,000 SBE/ml) no more reaction in the NPT.

In the quantitative prick test the actively patients demonstrated in comparison to the placebo group after 12 (p< 0.01) treated and 24 (p< 0.001) treatment-months a significant decrease of the skin reactivity. For the appraisal the quantitative skin-test became the area under the curve (AUC) the dose/ welt-area for the examined five allergen doses calculated and through the ratio to the histamine reaction put. While the active treatment with the mite allergoid itself decreased the reactivity in the comparison to the 1% histamine reference solution from 0.46 ± 0.32 by 0.22 ± 0.22 to 0.24 ± 0.24; with placebo on the other hand increased the AUC from 0.46 ± 0.32 by 0.39 ± 0.37 to 0.54 ± 0.47 (fig. 1).

Figure 1. Quantitative pricktest through the treatment-course [AUC] of the welt-area with Dermatophagoides pteronyssinus in relation to the welt-area with Histamine 1% (mean-value ± SEM) *** p< 0.001

Appraisal by the treating doctor
After 12 and 24 treatment-months certified the treating doctor significant changes (p< 0.05) in the health-status in the comparison of both groups. For 90% of the actively treated patients reported the treating doctor an improved or considerably improved health-status over the 2-year double blind phase (placebo 25-40%) deterioration was found only in the placebo group. After 3-years active therapy all 20 patients were a considerable improvement (75%) or respectively improvement (25%) entered.

**Visual analogue-chart and symptom medication score**

Data from the VAS and the SMS when multiple goal-size, evaluated as rank-sum-test, resulted in for the investigation-time period no significant differences with patients without demand for anti-symptomatic medication in the baseline-phase (active: 96.2 ± 10.9 (mean-value ± SEM) placebo 93.3 ± 0.7). With patients with demand for anti-symptomatic medication in the baseline phase, the more severe troubles against house-dust-mites demonstrated, could however a significant improvement under active versus placebo be verified (Acaroid®: 52.0 ± 9,8; placebo 89.3 ± 13,3; p < 0.05).

At the end of the first treatment-year one humbled demand at symptomatic medication was observable from the diary-notes of the patients, especially by the patient with bronchial troubles, that at the end of the second treatment-year led to a significant (p< 0.05) difference in favor of the immune-therapy (Fig 2).

Figure 2. Baseline adjusted medication score (mean-value ± SEM) through the treatment-course * p< 0.05

The group of asthmatics (n= 7) was for a sub-group-analysis of the efficacy according to Rhinitis/ Rhinoconjunctivitis and asthma too small, however demonstrated itself by the organ-symptoms (eye, nose, lung) in the lung symptom score a 66% improvement with respect to the exit-value in the Acaroid®-group (p= 0.77 versus Placebo) and simultaneous the most substantial decrease by the medications for the lower airways.