



Specific immunotherapy for rhinitis and asthma with a subcutaneous hypoallergenic high-dose house dust mite extract: results of a 9-month therapy

Aim: Effectiveness of a 9-month specific immunotherapy with a subcutaneous hypoallergenic high-dose house dust mite extract to reduce allergic symptoms as perceived by patients and physicians was assessed. **Patients & methods:** An observational, retrospective, multicenter study was carried out in patients diagnosed with asthma and/or rhinitis caused by house dust mites having started specific immunotherapy with Acaroid®. Primary end point was perceived effectiveness. **Results:** A total of 409 patients were included. According to physician-completed visual analogue scale, a 58.1% clinical improvement was observed. Patient-completed visual analogue scale showed a 69.8% clinical improvement. The need for unscheduled/emergency healthcare, as an indication of poor quality of life, showed a significant reduction. **Conclusion:** Our results confirm in a real-world setting the findings from randomized clinical trials of high-dose house dust mites allergoid immunotherapy with a subcutaneous hypoallergenic high-dose house dust mite extract.

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Keywords: asthma • house dust mite • quality of life • rhinitis • specific immunotherapy

The incidence and prevalence of IgE-mediated allergic respiratory diseases, such as allergic rhinitis and asthma has steadily increased in recent decades both in Western world [1] and in developing countries [2]. Worldwide, an estimate of 300 million individuals with asthma has been reported [3]. Management of allergic rhinitis [4] and asthma [5] result in important healthcare costs, particularly when poorly controlled [4,5].

House dust mites (HDMs; *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) are one of the most common indoor allergens [6], with levels of Der p 1, the major allergen of *Dermatophagoides pteronyssinus*, usually being higher than 10 µg/g of dust in some regions [7]; HDMs are an established cause of allergic respiratory diseases [6,8]. In fact, it has been suggested that HDMs are the main cause of allergic asthma in children [9], because HDMs are common in most regions

and in subtropical regions most allergic patients are sensitized to them [10–12]. They have been also found commonly in European regions, such as Germany or Northern Spain [13,14]. Reported proportions of asthmatic patients sensitized to HDM in various countries range from 45 to 85% [15]. A recent birth cohort study has shown that sensitization to HDM at age 2 is associated to asthmatic symptoms at age 12 [5], and exposure to HDM in infancy is significantly associated to subsequent asthma and the so-called ‘allergic march.’ A cross-sectional study has shown that 56% of patients with allergic rhinitis are sensitized to HDM [16]. It has been suggested that allergic rhinitis and allergic asthma are manifestations of the same disease, with 50% of patients with HDM-induced rhinitis showing HDM-induced asthma, and 95% of patients with HDM-induced asthma having HDM-induced rhinitis [17].

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Allergen avoidance by means of physical measures such as impermeable bedding, frequent vacuuming, heating or freezing has been promoted to prevent allergic diseases [16], but this has been difficult to achieve [18]. Chemical methods have also been recommended [6] and acaricide agents appear to be effective, but have a short-lived effect and could be unsafe [18]. Other avoidance methods such as changes in indoor environment may not be feasible in most cases [19,20]. Moreover, published studies have not shown clinical improvement with such methods [21,22] and two Cochrane reviews and meta-analyses have shown avoidance measures to be of no use in asthma [23] and of little benefit in rhinitis [24].

European guidelines have defined the methods for clinical trials in Allergen Immunotherapy (AIT), which has allowed high-quality research to be performed and rigorous evidence to be obtained in this field [25]. Several clinical trials have shown clinical effectiveness and safety of high-dose allergoid immunotherapy in HDM-allergic IgE-mediated allergic diseases [26,27]. A steroid-sparing effect has also been shown in children with asthma [26]. Randomized clinical trials provide the best evidence for the efficacy of a therapeutic agent. However, they usually include only selected, well-motivated and otherwise healthy patients to be treated in well monitored settings. Thus, generalization of their findings is not always easy or even feasible. Therefore, with efficacy of HDM-Subcutaneous Immunotherapy (SCIT) having been proved in clinical trials, real-world observational studies appear useful to describe therapeutic results in a wider, nonselected population of patients with allergic rhinitis/asthma.

We aimed at assessing effectiveness of a 9-month specific immunotherapy with a subcutaneous hypoallergenic high-dose house dust mite extract to reduce allergic symptoms as perceived by patients and physicians. Impact on quality of life and use of rescue medication and additional medical resources were also assessed.

Materials & methods

An observational, retrospective, multicenter study was carried out in Spain. The study was approved by the Ethics Committee at the Hospital Puerta del Mar in Cadiz, Spain on March 13, 2013 and classified by the Spanish Medicines Agency. Informed consent was obtained from patients or legal guardians. Patients diagnosed with asthma and/or rhinitis caused by HDM were included from September to December 2013, if they had started specific immunotherapy with Acaroid®, a subcutaneous hypoallergenic high-dose house dust mite extract. Rhinitis and asthma diagnoses were based on usual local methods in clinical practice.

Based on the existing perception in clinical practice of a quick response with Acaroid, we used a 9-months therapy instead of the usual 1-year therapy. Only one visit was performed after immunotherapy to fill a questionnaire by means of an interview with the investigator. The questionnaire can be found in Supplementary Data online. Baseline (pretreatment) data and data after a 9-month therapy with a subcutaneous hypoallergenic high-dose house dust mite extract were retrieved for comparison.

Acaroid (Merck - Allergopharma Joachim Ganzer KG, Reinbek, Germany) is a hypoallergenic depot allergoid preparation that contains high levels of powdered diafiltered HDM allergens (various mixed combinations of Der p 1, Der p 2, Der f 1 and Der f 2) [28]. Concentration is standardized in therapeutic units (TU) at two different strengths (1000 or 10,000 TU/mL). Content in µg/ml was Der p1 11.67, Der p2 10, Der f1 20, Der f2 15, respectively. Native allergens are modified with formaldehyde and glutaraldehyde to produce a hypoallergenic agent [28]. Such methods provide a marked reduction of allergenicity in skin testing or IgE-binding measured by RAST-inhibition [29], but do not reduce immunogenic activity and T-cell reactivity [30,31].

Primary end point was perceived effective based on a visual analogue scale (VAS) independently completed by patients and physicians (0–100, with 0 being the worst health state and 100 the best health state, regarding allergic disease). VAS was the same in all study sites. Secondary end points included changes in clinical symptoms intensity; and changes in use of scheduled and rescue medication, or unscheduled/emergency healthcare resources, as well as work/school absenteeism, as an indication of quality of life. Intensity of symptoms was classified as: 0, no symptoms; 1, rare (2 or fewer days per week); 2, common (2–5 days per week); 3, very common (more than 5 days per week). Such data are critical in the follow-up for immunotherapy; thus they are usually well entered in medical records. Also, medication data are routinely included in medical records in each visit.

Statistical methods

SAS System for Windows software package was used for all statistical procedures. A level of significance of 0.05 was used for all statistical tests, except in preliminary normalcy checking or variance homogeneity tests for which a level of 0.1 was used. Descriptive statistics were used for clinical and demographic variables. Between-groups comparison for VAS was based on Wilcoxon–Mann–Whitney test. No imputation for missing values was applied. Other between-group comparisons were done with unpaired Student t-tests

and chi-squared tests. Nonparametric tests were used for variables not showing a normal distribution based on a Shapiro–Wilks test. A Friedman test was used to assess temporal trends in symptoms and use of scheduled and rescue medication or healthcare resources.

Results

419 patients were included by 32 participating physicians. Two patients were later excluded due to noneligibility and final data were available for 401 patients. VAS data were not available in two patients before therapy and in 19 after therapy. Data on medication use were missing in 36 patients. Most patients (379) were mono-sensitized to HDM. The few poly-sensitized patients did not show relevant clinical manifestations related to non-HDM allergens. Mean (SD) age was 24.9 (14.4) years; 47.5% were men. A rhinitis diagnosis was found in 415 (99%) and an asthma diagnosis in 201 (48%). Moreover, 64.2% of patients had been diagnosed with conjunctivitis. Mean baseline FEV1 (%) was 88.3 (14.5) (88.5 in patients with rhinitis and 85.8 in patients with asthma). Demographic and baseline data are shown in Table 1.

Subcutaneous hypoallergenic high-dose house dust mite extract composition was 100% *D. farinae* in 2 (0.5%) patients; 100% *D. pteronyssinus* in 86 (20.5%) patients; and a 50–50 mix including both *Dermatophagoides* in 232 (55.4%) patients. Other proportions of both *Dermatophagoides* or unspecified mixes were used in the remaining patients.

A significant improvement in VAS was observed both for patient- and physician-perceived results. According to physician-completed VAS, a 58.1% clinical improvement was observed with a mean (SD) increase of 24.6 (22.4) (from 42.3 [21.3] to 66.9 [26.0]; $n = 401$, $p < 0.0001$ Friedman's test). Patient-completed VAS showed a 69.8% clinical improvement, with a mean (SD) increase of 26.8 (23.9) (from 38.4 [21.7] to 65.2 [26.0]; $n = 399$, $p < 0.0001$ Friedman's test).

In patients with rhinitis, according to physician-completed VAS a mean (SD) increase of 24.6 (22.4) [from 42.2 (21.3) to 66.7 (26.1); $n = 395$, $p < 0.0001$ Friedman's test] was observed. Patient-completed VAS showed a mean (SD) increase of 26.8 (24.0) [from 38.3 (21.8) to 65.1 (26.1); $n = 397$, $p < 0.0001$ Friedman's test]. In patients with asthma, according to physician-completed VAS a mean (SD) increase of 24.3 (21.8) (from 41.3 [19.4] to 65.6 [24.4]; $n = 192$, $p < 0.0001$ Friedman's test) was observed. Patient-completed VAS showed a mean (SD) increase of 27.4 (23.6) (from 37.5 [19.9] to 64.9 [24.3]; $n = 193$, $p < 0.0001$ Friedman's test). In patients aged ≤ 14 years, according to physician-completed VAS a mean (SD) increase of 5.8 (13.8) (from 44.6 [23.0] to 60.4 [28.0]; $n = 93$, $p < 0.0001$ Friedman's test) was observed. Patient-completed VAS showed a mean (SD) increase of 17.6 (15.9) (from 43.4 [23.4] to 61.2 [28.8]; $n = 94$, $p < 0.0001$ Friedman's test).

Baseline frequency and changes in individual clinical symptoms are shown in Table 2. Baseline ocular, nasal and bronchial symptoms were found in 76.1,

Table 1. Demographic and baseline data.

	Mean	SD
Age, years	24.9	14.4
	N	%
Sex		
–Men	199	47.5
–Women	220	52.5
Baseline diagnosis		
Rhinitis	415	99
– Unspecified	4	1.0
– Intermittent mild	18	4.3
– Intermittent moderate/severe	43	10.3
– Persistent mild	98	23.4
– Persistent moderate/severe	252	60.1
Asthma	201	48.0
– Unspecified	5	1.2
– Intermittent	112	26.7
– Persistent	84	20.0

99.0 and 51.4% of patients, respectively. After immunotherapy, an improvement was shown in 78.3, 84.5 and 72.6% of patients showing baseline ocular, nasal and bronchial symptoms, respectively (all $p < 0.0001$ Friedman's test). Out of 181 asthmatic patients who had bronchial symptoms before therapy, 131 (72.4%) showed a ≥ 1 severity step improvement with a reduction of steroid use based on GINA guidelines. Available data on IgE and specific IgE for HDM are shown in Table 4.

Use of scheduled medication was common at baseline (358 [85.4%] patients were taking at least one drug), and showed a significant reduction after immunotherapy (from 358 [85.4%] to 209 [52.1%]; $p < 0.0001$ Friedman's test). Baseline and final rescue medication use is shown in Table 3. A significant reduction was observed for oral antihistamines, bronchodilators, antiallergic eye drops and nasal steroids use. The need for unscheduled/emergency health-care, as an indication of poor quality of life, showed

Table 2. Baseline frequency and changes in individual clinical symptoms.				
Symptoms	Before immunotherapy		After immunotherapy	
	N	%	N	%
Ocular				
– No symptoms	94	23.9	193	51.5
– Uncommon	124	31.5	162	43.2
– Common	132	33.5	19	5.1
– Very common	44	11.2	1	0.3
Total	394	100.0	375	100.0
Improvement[†]				
– Yes			220	78.3
– No			61	21.7
Total			281	100.0
Nasal				
– No symptoms	4	1.0	52	13.1
– Uncommon	30	7.2	235	59.0
– Common	151	36.1	100	25.1
– Very common	233	55.7	11	2.8
Total	418	100.0	398	100.0
Improvement[†]				
– Yes			333	84.5
– No			61	15.5
Total			394	100.0
Bronchial				
– No symptoms	186	48.6	242	66.1
– Uncommon	82	21.4	97	26.5
– Common	91	23.8	24	6.6
– Very common	24	6.3	3	0.8
Total	383	100.0	366	100.0
Improvement[†]				
– Yes			135	72.6
– No			51	27.4
Total			186	100.0
[†] In patients with baseline symptoms. $p < 0.0001$, Friedman's test.				

a significant reduction, both for visits at emergency department (75.4% reduction; $p < 0.0001$) and for unscheduled specialist outpatient visits (73.5% reduction; $p < 0.0001$). Hospital admissions were also significantly reduced (from 1.2 to 0%; $p = 0.0253$); and work/school absenteeism showed a significant decline (84.4% reduction; $p < 0.0001$) (Figure 1).

Regarding safety, only one local adverse reaction was found.

Discussion

Our results confirm in a real-world setting the findings from randomized clinical trials of high-dose HDM allergoid immunotherapy with a subcutaneous hypoallergenic high-dose house dust mite extract in patients with allergic rhinitis and/or asthma. General health regarding respiratory allergy, as perceived by patients, showed a significant and substantial improvement, and such findings were corroborated by physicians' perception. An early response was observed. After 9-month therapy, specific ocular, nasal and bronchial clinical symptoms were markedly reduced from baseline levels. Significantly less drugs were needed, both for regular and rescue therapy. A significant reduction of both emergency and unscheduled visits suggests an improved quality of life. This is corroborated by the reduced rate of hospital admissions and work/school absenteeism. Use of drugs was significantly reduced, except for antihistamines which did not achieve a sig-

nificant difference, probably because patients with a long history use such drugs routinely and this is the last therapy to be changed. Steroid use reduction could also cause antihistamines to be maintained. The study therapy was safe.

Seasonal variations are unlikely to have had an impact on the results taking into account that many different Spanish with different climate and seasonal distribution were represented. Taking into account that immunotherapy requires a very strict follow-up, data on symptoms and medication use are usually well reported in medical records, and recall bias is probably low.

Our results corroborate previous findings. In a pivotal double-blind trial, Dokic *et al.* [27] found that, according to study physicians, the health condition of 90% of the actively treated patients had improved during a 2-year therapy. Specifically, in patients with more severe allergic reactions and needing symptomatic medication at baseline, a significant improvement compared with placebo could be demonstrated (52.0 ± 9.8 vs 89.3 ± 13.3 ; $p < 0.05$). The difference between groups in favor of immunotherapy reached statistical significance by the end of the second treatment year. In our real-world study a significant effect was already observed after 9 months, suggesting an early response. In another pivotal trial, Zielen *et al.* reported that mean daily dose decreased from 330.3 mg to 151.5 mg after 2 years of treatment [26]. Our results seem to confirm

Table 3. Baseline and final rescue medication use.

Rescue medication	Before immunotherapy		After immunotherapy		Reduction of use (p-value)
	N	%	N	%	
Oral antihistamines					0.0487
– Yes	271	64.7	244	60.8	
– No	148	35.3	157	39.2	
Total	419	100.0	401	100.0	
Bronchodilators					<0.0001
– Yes	160	38.2	122	30.4	
– No	259	61.8	279	69.6	
Total	419	100.0	401	100.0	
Eye drops					<0.0001
– Yes	48	11.5	21	5.2	
– No	371	88.5	380	94.8	
Total	419	100.0	401	100.0	
Nasal steroids					<0.0001
– Yes	173	41.3	107	26.7	
– No	246	58.7	294	73.3	
Total	419	100.0	401	100.0	

Table 4. Available data on IgE and specific IgE for house dust mites.				
		N	Mean	SD
Total IgE	Before therapy	245	435.6	478.8
	After therapy	116	327.9	493.5
<i>D. pteronyssinus</i> -specific IgE	Before therapy	275	47.6	42.7
	After therapy	135	36.8	33.2
<i>D. farinae</i> -specific IgE	Before therapy	253	55.3	266.0
	After therapy	131	27.0	30.2

such steroid-sparing effect. According to recent guidelines, the main objective in asthma therapy is control of respiratory symptoms, and prevent loss of lung function [32,33]. Available drugs for asthma and rhinitis treatment alleviate symptoms of rhinitis and asthma while administration is maintained, but such therapies do not modify immune mechanisms and do not alter the long-term course of the disease. Oral steroids are used to control symptoms and inhaled steroids achieve asthma control in most patients and are widely used [34]. However, this is not a curative treatment and causes side effects including pneumonia, oropharyngeal candidiasis and cough [32]. Thus, a therapy is needed to reduce the use of inhaled and oral steroids and prevent progression or even cure the disease.

AIT is based on the administration of increasing doses of an allergen extract until an optimal maintenance dose is achieved, and is the only therapy able to alter the natural course of IgE-mediated respiratory diseases because immune tolerance to the causative allergen is induced [35,36]. A number of double-blind, placebo-controlled clinical trials of AIT with various HDM extracts have shown clinical benefits [27,37–41], as has been highlighted in recent reviews [42–44].

AIT treatment has resulted in symptoms improvement, medication use reduction, bronchial hyper-responsiveness improvement and better quality of life [35,45–47]. AIT prevents progression of allergic rhinitis to asthma [48]. A sustained long-term effect is observed after treatment completion [49–51]. At present, some evidences suggest AIT could even prevent or cure respiratory allergy such as asthma [50,52]. Moreover, a steroid-sparing effect has been proved in adults with HDM-allergic asthma [3,53,54].

SCIT has been used for more than a century and it is effective in allergic asthma and rhinitis, as shown by Cochrane reviews [55,56] and meta-analyses [47,57,58]. AIT provides a disease-modifying effect in allergic diseases associated to HDM, as has been acknowledged for many years in international clinical guidelines [35,59]. AIT is considered to be an additional option in asthma therapy in current updates of guidelines by National Asthma Education and Prevention Program (NAEPP) [60], Allergic Rhinitis and its Impact on Asthma (ARIA) [61] and Global Initiative for Asthma (GINA) [32].

AIT based on high-dose modified HDM extracts has some important advantages compared with classical

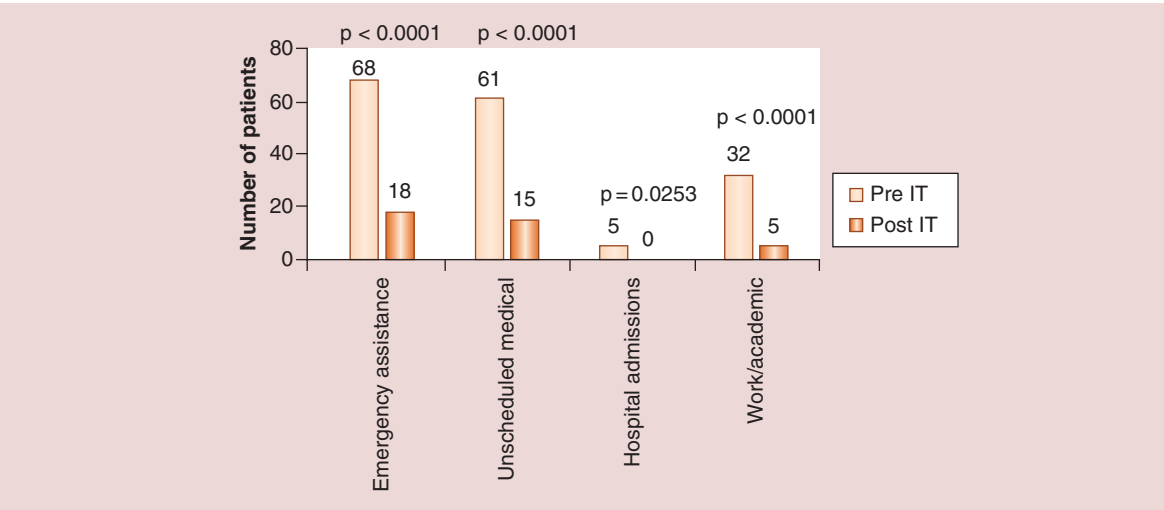


Figure 1. Use of unscheduled healthcare and absenteeism.
IT: Immunotherapy.

drug therapy. It is an etiological therapy specifically targeted to causative allergens. AIT appears to be effective from the first months of use, and long-term efficacy has been observed. According to European Medicines Agency (EMA), long-term efficacy refers to a relevant and prolonged benefit persistent after treatment is completed [25]. Mosbech and Osterballe first proved some decades ago that AIT effects can persist after therapy completion [62]. Contrary to conventional drug treatments, a favorable impact from HDM-based AIT can persist after the therapeutic cycle has been completed.

Moreover, AIT has preventive effects on the development of new sensitizations to additional allergens. In fact, early start of AIT has been suggested in order to avoid chronic irreversible lung changes [63]. Taking into account that patients should be asymptomatic and stable when AIT is started, a simultaneous or even previous onset of symptomatic drug therapy can be useful.

Our study has as an obvious limitation the absence of a placebo group, but being a retrospective study this was unavoidable. However, the evaluation of clinical efficacy data, remarkably high, should be tempered by this fact. Also, not all patients received the same product under the label Acaroid.

Only randomized trials can provide high level evidence on efficacy and safety. However, real-world observational studies provide a complementary knowledge based on a large number of patients treated in a real clinical setting. Our study includes data on global VAS evaluation, and also on specific nasal, ocular and bronchial symptoms, which is uncommonly reported in previous studies.

Conclusion

In conclusion, our results confirm existing evidences suggesting that high-dose allergoid immunotherapy with a subcutaneous hypoallergenic high-dose house dust mite extract in patients with allergic rhinitis and/or asthma can improve perceived effectiveness, and can reduce clinical symptoms. Moreover, quality of life can be enhanced, as suggested by a lower requirement of medication and unscheduled healthcare.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- A significant improvement was observed both for patient- and physician-perceived results in patients with allergic rhinitis/asthma receiving a 9-month specific immunotherapy with a subcutaneous hypoallergenic high-dose house dust mite extract.
- After immunotherapy, a significant improvement was shown in baseline ocular, nasal and bronchial symptoms.
- The need for unscheduled/emergency healthcare, as an indication of poor quality of life, showed a significant reduction, both for visits at emergency department and for unscheduled specialist outpatient visits.
- Hospital admissions were significantly reduced and work/school absenteeism showed a significant decline.

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