Association Between Component-Resolved Diagnosis of House Dust Mite Allergy and Efficacy and Safety of Specific Immunotherapy

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Component-resolved diagnosis (CRD) has modified the accuracy of the diagnosis of respiratory allergy and prescription of specific immunotherapy (SIT) [1,2]. CRD has demonstrated the presence of minor allergens in SIT extracts and their role in some adverse effects of SIT [2,3]. Its association with the efficacy of SIT has not been tested. Our objective was to assess the possible association between the clinical efficacy of a *Dermatophagoides pteronyssinus* SIT extract and sensitization to mite allergens in a group of patients with respiratory allergy induced by house dust mite (HDM).

We performed a retrospective post hoc analysis of the efficacy and safety of a SIT study previously carried out by our group [4,5] with currently available HDM-based CRD. Our previous study was a prospective, phase 4, randomized, controlled study with a 5-year follow-up period. A total of 142 patients aged 5-45 years with HDM-induced respiratory allergy received SIT extract (Pangramin Depot UM, ALK-Abelló, 10 UB/mL; Der p 1, 4 µg/mL; and Der p 2, 2 µg/mL) for at least 3 years. Adherence to SIT was good. Clinical evaluations and blood samples obtained before initiation of SIT were available for 84 patients. Differences in baseline characteristics between good and poor adherers were ruled out [5]. Efficacy and safety data have been published elsewhere [4,5]. Diagnosis and the indication for SIT were based on compatible symptoms and positive skin test and specific IgE results. Blood samples were aliquoted and stored at –20°C before use. Serum levels of the components of *Dermatophagoides pteronyssinus* (Der p 1, Der p 2, Der p 10, and Der p 23, [ImmunoCAP Thermo Fisher Scientific] and Lep d 2 [AdviaCentaur]) were determined simultaneously.

CRD results were grouped per patient in allergen profiles (see Venn diagram in Supplementary Material). The profiles

Table. Association Between the Clinical Efficacy and Safety of Specific Immunotherapy and Baseline Sensitization to Mite Allergens

Group Profile Clinical Efficacy at Third Year	VAS3 Score Changes	EVG3 Score Changes	*P* Value VAS3	*P* Value EVG3
A	70.4%	75.9%	.741	.469
B	65.2%	83.3%		
C	57.1%	62.5%		
Der p 23 <0.35, kU/L	7 (77.8%)	44 (69.8%)	1	–
Der p 23 >0.35, kU/L	4 (44.4%)	52 (82.5%)	–	.022
Clinical Efficacy at Fifth Year	VAS5 Score Changes	EVG5 Score Changes	*P* Value VAS5	*P* Value EVG5
A	75.9%	81.5%		
B	78.3%	91.7%	.931	.415
C	71.4%	75%		
Der p 23 <0.35, kU/L	7 (77.8%)	44 (69.8%)	1	–
Der p 23 >0.35, kU/L	8 (88.9%)	54 (83.1%)	–	1
Safety Data and Allergen Profile Individual Profile[a]		Group Profile	Adverse Event	
Der p 1; Der p 2; Lep d 2; Der p 10; Der p 23 (units, kU/L)				
Der p 1, 7.93; Der p2, 16.3; Lep d 2, 0; Der p 10, 0; Der p 23, 2.41		A	Local reaction	
Der p 1, 14.2; Der p 2, 15.3; Lep d 2, 3.92; Der p 10, 0; [b]Der p 23		B	Anaphylaxis	
Der p 1, 42.7; Der p 2, 40.5; Lep d 2, 0; Der p 10, 0; Der p 23, 44.4		A	Nodes	
Der p 1; 0.46; Der p 2, 6.52; Lep d 2,0; Der p 10, 0; Der p 23, 0.45		A	Unspecified symptoms	
Der p 1, 0.01; Der p 2, 0.39; Lep d 2, 0.01; Der p 10, 0.33; Der p 23, 0		C	Rhinoconjunctivitis	
Der p 1, 27.9; Der p 2, 9.98; Lep d 2,0.01; Der p 23, 5.34			Local Reaction	
Der p 1, 25; Der p 2, 21.6; Lep d 2, 0.23; Der p 10, 0; Der p 23, 16.2		B	Unspecified symptoms[c] Bronchial asthma[c]	
Der p 1, 0.09; Der p 2, 9.33; Lep d 2, 2.58; Der p 10, 0.03; Der p 23, 19.7		B	Bronchial asthma	
Der p 1, 18.3; Der p 2, 18.1; Lep d 2, 0.05; Der p 10,0; Der p 23, 2.88		A	Asthma	
Der p 1, 8.19; Der p 2, 7.66; Lep d 2, 0.03; Der p 10, 0; Der p 23, 3.48		A	Local Reactions	
Der p 1, 25.6; Der p 2, 44.1; Lep d 2, 0; Der p 10, 0; [b]Der p 23		A	Rhinoconjunctivitis	

A, Positive Der p 1 and/or Positive Der p 2; B, Positive Lep d 2 and at least 1 major *Dermatophagoides pteronyssinus* allergen; C, Der p 10 sensitization and/or negative Der p 1-Der p 2. VAS3, visual analog score at third year; VAS5, visual analog score at fifth year; EVG3, combined global score of symptoms and medication at third year; EVG5, combined global score of symptoms and medication at fifth year.
[a]Five patients (4 with local reactions and 1 with unspecified symptoms could not be profiled due to the lack of an available baseline blood sample). First column details patients' individual sensitization to mite allergens.
[b]Blood sample was not sufficient for Der p 23 determination.
[c]Symptoms present in the same patient, but not simultaneously.

were agreed between authors after taking day-to-day practice and sample size into account. The analysis was based on 3 profiles: A, sensitization to Der p 1 and/or Der p 2 as major allergens and their quantification in SIT extract; B, cosensitization to Lep d 2 and major HDM allergens, as *Lepidoglyphus* species, which is prevalent in our area [6]; and C, absence of sensitization to major mite allergens/ Der p 10 sensitization.

Der p 23 values were analyzed alone, since their role in the diagnosis of mite allergy and presence in SIT extracts has not yet been defined. Nonresponse to SIT was defined as changes below 30% at the third and fifth years, as proposed by Malling [7] measured using a visual analog scale (VAS) and/or the Global Score of Combined Rhinitis and Asthma Symptoms and Rescue Medication (EVG) [5]. The allergenic profiles of patients who developed AEs during SIT were described in detail. The analysis was performed using SPSS 22.0 for Windows (IBM Corp). Rates of response were analyzed using the χ^2 test. Statistical significance was set at $P<.05$.

Profiles A, B, and C were observed in 54, 23, and 7 patients respectively. Nonresponse rates in the third year were 29.6%, 34.8%, and 42.9% by VAS ($P=.741$) and 24.1%, 21.7%, and 28.6% by the EVG score ($P=.931$). Nonresponse rates at the fifth year were 24.1%, 21.7%, and 28.6% by VAS ($P=.469$) and 18.5%, 8.3%, and 25% by the EVG score ($P=.415$). Eighty-eight percent of patients were sensitized to Der p

23 (specific IgE > 0.35 kU/L). At the third year, there was a significant association between clinical efficacy variables and sensitization to Der p 23 (*P*=.03), although the association had disappeared at the fifth year. Two patients who experienced an asthma episode and the patient who experienced an anaphylaxis episode during administration of SIT were sensitized to Lep d 2.

The German Immunotherapy Guideline includes relevant allergenic components in the diagnosis of pollen allergy and recognizes their role in the evaluation of polysensitized patients [8]. The EAACI Molecular Allergology User's Guide includes decision algorithms for SIT prescription in pollen allergies [2]. Knowledge on major mite allergens is increasing, as is knowledge on the association between the 3 profiles and demographic and diagnostic data [2,9]. However, the indication of SIT in mite allergy relies on complete extract-based IgE determinations [2].

Current CRD data may have led to discrepancies in the indication for SIT extracts or their composition in 36% of cases. Eight percent of patients would not have been prescribed SIT owing to negative results for major mite allergens or Der p 10. Despite the limited number of patients, efficacy data suggest the importance of additional allergens to those requested for diagnosis. Their presence in the SIT extract should have induced a clinical improvement. Sensitization to Der p 23 (88%) in the sample was more frequent than sensitization to the A profile. However, its role in diagnosis of mite allergy [2] and quantification in SIT extracts has yet to be determined. The differences observed in clinical scores at the third year in Der p 23–positive patients were absent at the fifth year.

Twenty-eight percent of the sample were sensitized to Lep d 2, suggesting at least in vitro cosensitization by both species. We did not observe an association between nonresponse to SIT and sensitization to Lep d 2, although 13% of profile B patients experienced systemic reactions during treatment, as opposed to 5% of profile A patients.

The most frequent profile included sensitization to at least 1 major mite allergen and corresponds to the profile in which mite SIT efficacy is expected. In addition, the SIT extract used provided information about the quantity of both allergens.

We performed a retrospective analysis of HDM-based CRD and its association with clinical efficacy and safety. The indication for SIT and randomization were based on the objectives of previous studies [4,5]. Our analysis was restricted to patients with complete data on clinical efficacy variables and available serum samples. Our results are valid, although the sample size is limited. Retrospective studies enable us to put forward hypotheses that should be confirmed in studies with more appropriate designs. Thus, Melioli et al [10] suggested performing prospective studies in which standard diagnosis, component-based diagnosis, and the subsequent indication for immunotherapy were randomized to validate the role of CRD in SIT and, consequently, in its efficacy [10].

In conclusion, we found no association between the clinical efficacy of SIT based on HDM and sensitization to mite allergens. The indication for SIT based on sIgE to a *D pteronyssinus* extract enabled us to make an accurate diagnosis and prescribe SIT in this group of patients. However, the role of Lep p d 2 as a possible risk factor for systemic reactions during SIT should be explored in the future.

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Conflicts of Interest

EA has received speaker's honoraria from ALK-Abelló and travel support from ALK-Abello, Leti, Roxall, and HAL.

SE has received travel support from LETI, Roxall, and Immunotek.

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Previous Presentations

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References

1. Sastre J, Sastre-Ibañez M. Molecular diagnosis and immunotherapy. Curr Opin Allergy Clin Immunol. 2016;16(6):565-70.
2. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, et al. EAACI Molecular Allergology User's Guide. Pediatr Allergy Immunol. 2016 ;27 Suppl 23:1-250. doi: 10.1111/pai.12563.
3. Alcántara M, Sáenz de San Pedro B, Cañada C, Muñoz MA, Jimeno L, Villalba M et al. Steps Towards Clarifying the Clinical Relevance of Minor Olive Allergens in Areas With Extremely High Levels of Olive Pollen. J Investig Allergol Clin Immunol. 2017;27(2):138-40.
4. Tabar AI, Echechipía S, García BE, Olaguibel JM, Lizaso MT, Gómez B, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus. J Allergy Clin Immunol. 2005;116(1):109-18.
5. Tabar AI, Arroabarren E, Echechipía S, García BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. J Allergy Clin Immunol. 2011 ;127(1):57-63.
6. Barber D, Arias J, Boquete M, Cardona V, Carrillo T, Gala G, et al. Analysis of mite allergic patients in a diverse territory by improved diagnostic tools. Clin Exp Allergy. 2012;42(7):1129-38.
7. Malling HJ. Immunotherapy as an effective tool in allergy treatment. Allergy. 1998;53(5):461-72.

8. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int. 2014;23(8):282-319.
9. Dominguez-Ortega J, Delgado J, Blanco C, Prieto L, Arroabarren E, Cimarra M, et al Specific allergen immunotherapy for the treatment of allergic asthma: a review of current evidence. J Investig Allergol Clin Immunol. 2017;27(Suppl. 1):1-35.
10. Melioli G, Savi E, Crivellaro MA, Passalacqua G. Potential of molecular based diagnostics and its impact on allergen immunotherapy. Asthma Res Pract. 2016 Jun 2;2:9. eCollection 2016.

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