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Limited impact of Der p 23 IgE on treatment outcomes in tablet allergy immunotherapy phase III study

To the Editor,

Allergen 23 from *Dermatophagoides pteronyssinus* (Der p 23) has recently been identified as a novel major house dust mite (HDM) allergen based on the high prevalence of Der p 23-specific IgE in HDM-sensitized individuals.[1] The clinical importance of Der p 23 sensitization is unknown. It could be important for accurate diagnosis and for efficacy of HDM allergy immunotherapy (AIT). To address these issues, the sensitization pattern towards HDM allergens in a clinical trial population with established HDM allergic asthma was analysed retrospectively. This allowed examination of immunological and clinical effects of sublingual immunotherapy (SLIT) with the SQ HDM SLIT-tablet (ALK-Abelló A/S) in relation to Der p 23 sensitization status.

The MITRA trial included 834 subjects with HDM allergic asthma. Primary end point was time to first asthma exacerbation.[2] Allergen-specific IgE (Der p 1, 2, 10 and 23) were determined in the MITRA trial population at baseline.[2] IgG4 to Der p 1, 2 and 23 was measured in the same subjects at baseline and end of trial. Antibody levels were measured by ImmunoCAP (Thermo-Fisher). Allergen content of the SQ HDM SLIT-tablet was analysed by mass spectrometry. Der p 1 and Der p 23 content was measured by ELISA (Indoor Biotechnologies, Charlottesville, VA; EPC-DP23-X and EPC-DP1-X). See MITRA Summary table and descriptions of MS- and statistical analyses in the Supporting information.

The prevalence of Der p 1, 2, 23 and 10 sensitization was determined to be 78%, 86%, 66% and 5%, respectively, which is in accordance with other populations.[1,3-6] Only a small proportion of individuals was sensitized to only one of the four allergens (Figure 1A). This matches previous longitudinal birth cohort data showing that development of HDM sensitization is characterized by concomitant sensitization to Der p 1, 2 and 23 early in life. These allergens, as a group, dominate the further evolution of the HDM IgE sensitization patterns.[7] Consequently, it has been suggested that inclusion of Der p 23 could improve the diagnostic value of component-resolved diagnosis for HDM allergy.[4] The majority of the HDM-sensitized individuals in the MITRA trial (92%) was identified by testing for IgE towards Der p 1 and/or 2. Further inclusion of Der p 23 sensitization identified only 2% more patients, that is to 94% (Figure 1A, red columns). The mean level of Der p 23 IgE in the MITRA population is 2.5- to 3.5-fold lower compared with Der p 1 and 2, and even below the level of IgE specific for the minor allergen Der p 10 (Figure 1B). A similar observation was made in a different population.[3]

A typical and robust biomarker of exposure to the respective allergen during AIT is the treatment-mediated induction of allergen-specific IgG4.[8] Allergen-specific IgG4 towards Der p 1, 2 and 23 before and after SQ HDM SLIT-tablet treatment in Individuals with (IgE+) or without IgE (IgE-) (cut-off = 0.7 kU_A/L) towards individual HDM major allergens at baseline was measured. In subjects with major allergen-specific IgE ≤ 0.70 kU_A/L at baseline, no increase in specific IgG4 was observed (Figure 1C, left-hand panels). A significant increase in allergen-specific IgG4 as a result of treatment was seen in subjects with baseline major allergen-specific IgE levels of ≥0.70 kU_A/L (Figure 1C, right-hand panels).

The primary end point of the MITRA trial was time to first moderate or severe asthma exacerbation during inhaled corticosteroid (ICS) reduction (assessed over a 6-month period at the end of the trial where ICS was reduced by 50% for 3 months and then completely withdrawn for 3 months), which was met for both active doses of 6 and 12 SQ-HDM.[2] The forest plot in Figure 1D shows the results of sub-group *post hoc* analyses of the clinical effect in relation to the subjects' Der p 23 sensitization status at baseline. In the group of subjects with or without Der p 23 at baseline, there was a statistically significant effect on the hazard ratio for asthma exacerbations compared with the placebo group (Line A). In contrast, no statistically significant differences between active and placebo were observed in the two sub-groups of subjects without or with Der p 23 IgE at baseline, respectively (Lines B and C). Thus, the existence of Der p 23 IgE at baseline did not impact clinical efficacy of SQ HDM SLIT-tablet treatment (Figure 1D).

An additional analysis investigating the probability of subjects experiencing the first asthma exacerbation at a given time point during the efficacy assessment period based on Der p 23 sensitization status was performed (Figure 1E, red curves). There was no statistically significant difference between Der p 23 IgE-positive and negative subjects in the placebo group (Figure 1E, blue curves). Therefore, IgE sensitization to Der p 23 neither affects the time to first asthma exacerbation nor the likelihood of treatment response. A similar conclusion was made from a small HDM subcutaneous AIT (SCIT) trial where no association between the clinical efficacy of SCIT and sensitization to individual mite allergens was found.[9]

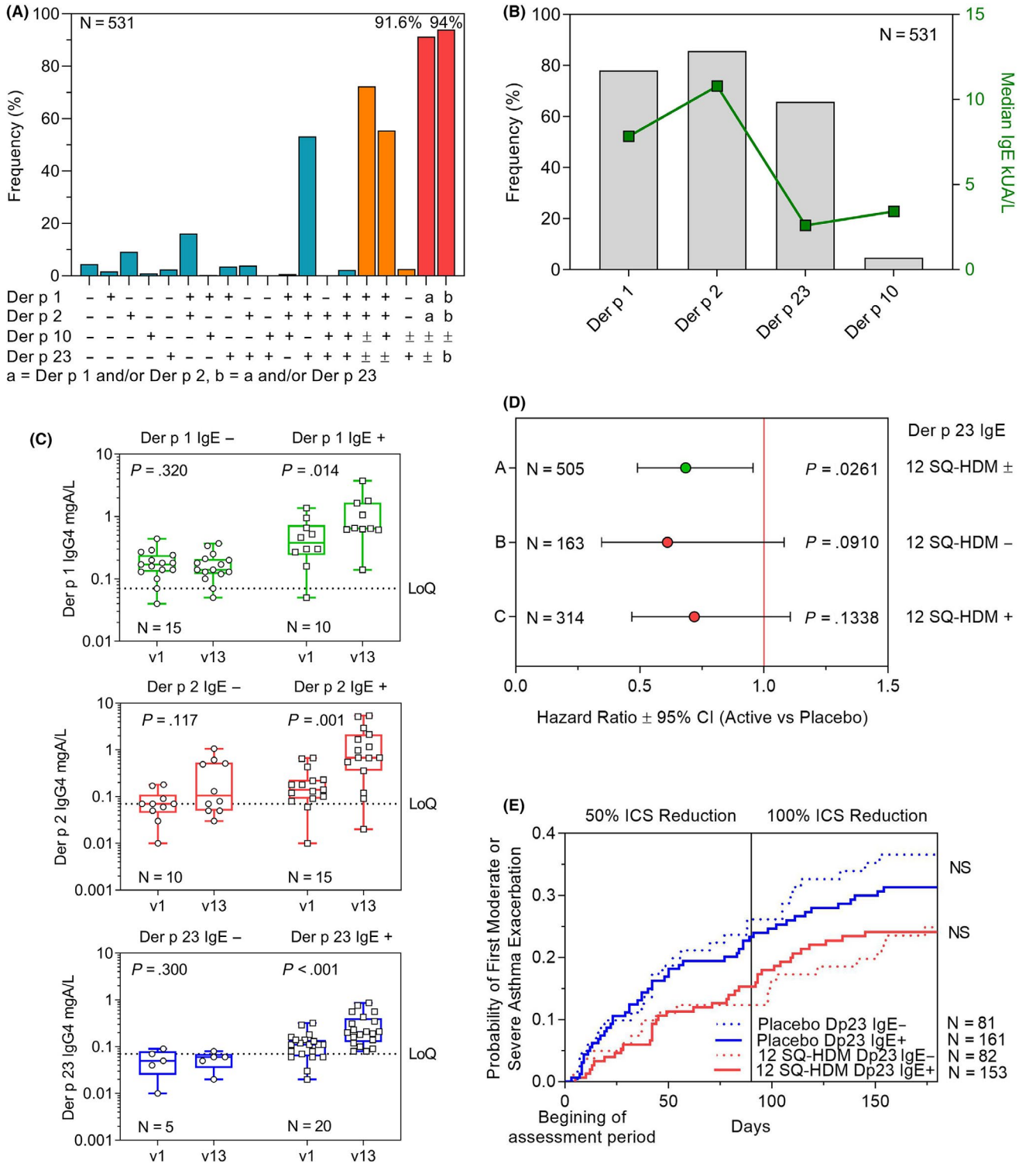

FIGURE 1 A, IgE sensitization frequencies: Der p 1, Der p 2, Der p 10 and Der p 23 (blue), combined Der p 1 and Der p 2 sensitization with and without Der p 10 and Der p 23 (orange, red). B, Sensitization frequencies (columns), allergen-specific IgE concentration (green squares). C, baseline IgG4 (v1), end of trial (v13). D, Clinical effect A: Der p 23±, active (12SQ-HDM) vs placebo; B: Der p 23-, active (12SQ-HDM) vs placebo; and C: Der p 23+, active (12SQ-HDM) vs placebo. E, Probability of time to first asthma exacerbation (12SQ-HDM, Placebo). +:allergen-specific IgE > 0.7kU$_A$/L; −:allergen-specific IgE < 0.7kU$_A$/L. a:Der p 1 and/or Der p 2 IgE; b:Der p 1 and/or Der p 2 and/or Der p 23 IgE. CI, confidence Interval; Dp23, Der p 23; LoC, line of quantification; NS, nonsignificant

The allergen content of the *Dermatophagoides pteronyssinus* extract used in SQ HDM SLIT-tablet was analysed by qualitative mass spectrometry (MS) analyses which demonstrated a broad representation of HDM allergens (Table 1). The content of Der p 23 relative to Der p 1 was furthermore determined by ELISA. In three independent *Dermatophagoides pteronyssinus* tablet extract

TABLE 1 *Dermatophagoides pteronyssinus* allergens identified in the SQ HDM SLIT-tablet extract by mass spectrometry. See online repository for analytical details

Allergen	Biochemical name[a]	MW (kDa)[b]	# of identified peptides	Sequence coverage (%)¨
Der p 1	Cysteine protease	25	17	55
Der p 2	NPC2 family	14	12	94
Der p 3	Trypsin	25	19	51
Der p 4	Alpha-amylase	57	12	26
Der p 5	-	14	3	18
Der p 6	Chymotrypsin	25	7	40
Der p 7	Bactericidal permeability-increasing like protein	22	19	56
Der p 8	Glutathione S-transferase	26	8	25
Der p 9	Collagenolytic serine protease	27	10	43
Der p 10	Tropomyosin	33	19	64
Der p 11	Paramyosin	102	5	6
Der p 13	Cytosolic Fatty Acid Binding Protein	15	11	58
Der p 14	Apolipophorin	191	41	24
Der p 15	Chitinase-like protein	59	11	16
Der p 18	Chitin-binding protein	49	6	15
Der p 20	Arginine kinase	40	17	43
Der p 21	-	15	1	9
Der p 23	Peritrophin-like protein domain (PF01607)	8	6	57
Der p 24	Biquinol-cytochrome c reductase binding protein	14	n.d.	-
Der p 25	Triosephosphate isomerase	27	15	71
Der p 36	-	22	9	47
Der p 37	Petrotrophic-like protein domain	26	3	13
Der p 38	Bacterial lytic enzyme	14	6	46

Note: Several isoallergens were identified from most allergen groups, but for simplicity, sequence coverage is based on only isoallergen × .0101 from each allergen group.

Abbreviation: n.d., not detected.

[a]*Source:* IUIS/allergen.org.

[b]Theoretical average mass for mature allergens (ie excluding signal or pro peptides) and without PTMs.

batches, Der p 23 was shown to constitute the equivalent of 25.8%-26.1% of Der p 1 on a molar scale. That the Der p 23 content in the SQ HDM SLIT-tablet extract is significant as well as immunologically relevant is supported by the data in Figure 1C which clearly demonstrates that Der p 23 is available in sufficient amounts to efficiently induce a Der p 23-specific IgG4 response in subjects sensitized to Der p 23 at baseline.

Based on our observations in this cohort, inclusion of baseline Der p 23 IgE measurements only marginally increased (from 92% to 94%) the identification of HDM-sensitized individuals relative to Der p 1 and 2 IgE alone. The induction of Der p 23-specific IgG4 during treatment demonstrates that the SQ HDM SLIT-tablet contains immunologically relevant amounts of all three HDM major allergens. However, in this well-characterized cohort of HDM allergic asthma patients there was no measurable influence of the Der p 23 sensitization status at baseline on the clinical effect, and stratification of patients based on Der p 23 sensitization before initiating AIT does therefore not appear to be clinically relevant.

KEYWORDS

cinical effect, Der p 23, diagnosis, HDM SLIT-tablets

CONFLICT OF INTEREST

TS, HI, LHC, NJ, KL and PSJ are ALK A/S shareholders. TS, HI, LHC, NJ and PSJ are employees of ALK A/S. KL is a consultant for ALK A/S.

AUTHOR CONTRIBUTIONS

HI, LHC, NJ and TS contributed to data acquisition. TS, PSA, HI, NJ and LHC contributed to experimental designs. TS, HI, LHC, TE, NJ, KL and PSA contributed to data interpretation and preparation of the manuscript. The final version of the manuscript was approved by all authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Combined analysis of transcriptomic and genetic data for the identification of loci involved in glucocorticosteroid response in asthma

To the Editor,

An increasing number of therapies are available to treat asthma, but inhaled corticosteroids (ICS) are still the most commonly prescribed and effective controller asthma medication.[1] Both environmental and genetic factors are involved in ICS response. However, few biomarkers have been associated with response to