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Reply to “Inferring clinical relevance of der p 23 from the restricted effect on treatment outcomes after tablet allergy immunotherapy”

We appreciate the comments made by Drs. González-Pérez and Poza-Guedes to our paper “Limited impact of Der p 23 IgE on treatment outcomes in tablet allergy immunotherapy phase III study¹” and would like to provide some clarification.

Drs. González-Pérez and Poza-Guedes raise four points of concern related to our paper:

1. “Accurate knowledge of the house dust mite (HDM) allergens in the environment is decisive in the prescription of effective allergen immunotherapy (AIT).”

Patients indeed respond to allergens in the environment, but very heterogeneously. Thus, in line with common clinical practice, we find that rather than accurate knowledge of individual patients' local allergen environment, diagnosis based on sensitization pattern and patient history (anamnesis) is decisive for the prescription of effective allergen immunotherapy (AIT).

2. “The retrospective post hoc observation of a missing association between the clinical efficacy of AIT and sensitization to individual mite allergens in a cohort of HDM allergic asthma patients, should be cautiously interpreted.”

When conducted and presented with full transparency regarding trial population, trial medication and methods etc as in our original paper,¹ post hoc analyses are valuable for hypothesis generation. However, the inherent limitations that exist for all post hoc subgroup analyses always necessitate cautionary interpretation of the results. Replication of our post hoc analyses data in an adequately designed confirmatory trial would of course be ideal.

3. “the inclusion of an additional arm in the study protocol, of patients treated with a HDM tablet comprising a represented and standardized source of Der p 23 -quantified in SQ-HDM units, not limited to a molar-scale determination seems essential to a preferred assessment of the clinical (primary outcome) and immunological (secondary outcome) effects of this allergen upon uncontrolled asthma.”

A 12 SQ-HDM SLIT-tablet contains certain amounts of Der p/f 1 and 2 that can be measured in µg/tablet.² Likewise, in the current study, the content of Der p 23 in the SQ HDM SLIT-tablet extracts was demonstrated by MS and quantified by ELISA, thereby confirming the presence of all three HDM major allergens in the SQ HDM SLIT-tablet. It is furthermore important to note that SQ-HDM is not a unit that can be applied to individual allergens in an extract. In addition to allergen content, the SQ-HDM unit comprises the combined total allergenic activity of all allergens present in the extract (including Der p 23), based on the reactivity of the extract towards a standardized pool of HDM sensitized patients' sera. Therefore, similar to Der p/f 1 and Der p/f 2, the Der p 23 content and contribution to the extract's total allergenic activity were taken into account in the study.

4. “the greater dose-dependent increases observed in allergen-specific IgG4 to *D. pteronyssinus* for Der p 1 and Der p 2 compared to the Der p 23-specific IgG4 responses, suggests that although this allergen is present, may be underrepresented in the intended HDM SLIT tablet.”

As reported by us and others, Der p 23 gives rise to lower levels of IgE compared with Der p 1 and Der p 2 despite high prevalence of sensitization.^{1,3} It is therefore not surprising that also a more modest IgG4 response towards Der p 23 compared with Der p 1 and Der p 2 is seen during AIT.

To the best of our knowledge, no standardised reference for the content of group 23 allergens in HDM extracts exists that in a meaningful way could indicate over- or underrepresentation of Der p 23. We favour the interpretation that the level of Der p 23 specific IgG4 induced by AIT reflects the inherent immunogenicity of the allergen. Further, despite several investigations IgG4 levels have not yet been shown to predict the clinical effect of AIT but is rather considered a biomarker of exposure to allergen.⁴

The data provided in our original paper¹ were obtained from a clinical trial conducted in a population diagnosed according to current medical practice who, during the course of the trial, responded clinically to natural HDM exposure. Subjects in the active arm of the trial received treatment with the SQ HDM SLIT-tablet

containing a defined and immunologically active amount of Der p 23. With the inherent limitations of post hoc analyses, our findings that Der p 23 sensitization status at baseline had no measurable influence on the clinical effect of HDM AIT in this trial and that stratification of patients based on Der p 23 sensitization before initiating AIT did not appear to be clinically relevant provide an important contribution to the understanding of the role of Der p 23 in HDM AIT.

On behalf of all co-authors.

CONFLICT OF INTEREST

HI, LHC, NJ, KL and PSJ are ALK A/S shareholders. TS, LHC, NJ and PSJ are employees of ALK A/S. HI and KL are consultants for ALK A/S. Dr Eiwegger reports other from DBV, grants from Innovation fund Denmark, Regeneron, outside the submitted work; investigator initiated oral immunotherapy trials supported by the Allergy and Anaphylaxis Program Sickkids; associate editor for Allergy. Thomas Eiwegger receives a grant outside the submitted work from ALK A/S. Local advisory board ALK A/S. In kind contributions from MacroArray Diagnostics outside of the submitted work.

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REFERENCES

1. Stranzl T, Ipsen H, Christensen LH, et al. Limited impact of Der p 23 IgE on treatment outcomes in tablet allergy immunotherapy phase III study. *Allergy*. 2020; <https://doi.org/10.1111/all.14200>. [Epub ahead of print].
2. Ohashi-Doi K, Kito H, Du W, et al. Bioavailability of house dust mite allergens in sublingual allergy tablets is highly dependent on the formulation. *Int Arch Allergy Immunol*. 2017;174:26-34.
3. Mueller GA, Randall TA, Glesner J, et al. Serological, genomic and structural analyses of the major mite allergen Der p 23. *Clin Exp Allergy*. 2016;46:365-376.
4. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI position paper. *Allergy*. 2017;38:42-49.