

Sublingual immunotherapy with house dust mite tablets in children—The evidence-based journey of allergen immunotherapy proceeds

In this issue, Keisuke Masuyama and coworkers report recent results of a multicenter double-blind, placebo-controlled (DBPC) Phase III trial on both clinical efficacy and safety of house dust mite (HDM) sublingual immunotherapy (SLIT)-tablets in Japanese pediatric and adolescent patients with moderate-to-severe HDM-related allergic rhinitis (AR).¹ The importance of this work refers to its novelty regarding clinical data on this preparation in children in the age of 5–11 years with HDM AR.

Keynotes of the article by Masuyama et al.¹

- Clinical study results from a multicenter (DBPC) Phase III trial of HDM SLIT tablets in 458 Japanese pediatric and adolescent patients with moderate-to-severe HDM AR
- Treatment course of one year with active (10 000 Japanese allergy units, equivalent to 6 SQ-HDM in Europe and the United States) or placebo SLIT treatment with tablets
- Treatment effect size of 21% in the pediatric (5–11 years) and 26% in the adolescent population (12–17 years) for the primary endpoint
- Clinical efficacy also demonstrated for several secondary endpoints
- Safety profile comparable to data reported so far for HDM SLIT tablets in adolescents and adults
- First robust randomized DBPC confirmatory (Phase III) trial to demonstrate statistically significant and clinically relevant efficacy of HDM SLIT tablets in AR in children under the age of 12 years

After the scientific inauguration of allergen immunotherapy (AIT) by Noon and Freeman more than 100 years ago, the merits of this causal treatment with immunomodulating properties have been widely investigated in clinical trials and AIT broadly used in the daily clinical routine of allergists all over the world. The European Academy of Allergy and Clinical Immunology (EAACI) has recently published multiple systematic reviews on AIT in different indications such as allergic rhinoconjunctivitis² and several clinical AIT guidelines

on the basis of the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach.³ The aim of the guidelines was to provide evidence-based recommendations for clinical care following the Oxford Centre for Evidence-based Medicine methodology.⁴

In the guideline on AIT in allergic rhinoconjunctivitis,⁵ the authors reported for SLIT a grade A recommendation for short-term benefits of HDM tablets for “children and adolescents” based on one North American⁶ and one Japanese⁷ clinical trial with mixed age groups (adolescent and adult patients). Due to a lack of published data for long-term efficacy of HDM tablets in this age group, a grade C recommendation was given for this indication as extrapolated from adult data.⁵ Taken together, the guideline's analysis and recommendation underpin the importance of further clinical evaluation of AIT in AR related to HDM especially in the pediatric population.

Even so, results from Phase II/III clinical trials of HDM SLIT with mixed populations of adolescent and adult HDM AR patients performed in Europe,⁸ North America,⁶ and Japan⁷ are available demonstrating sufficient efficacy for HDM tablets in these age groups (Table 1⁹). In a recently published post hoc, pooled analysis of the North American and Japanese trials, the data on efficacy and safety in the subgroup of adolescent patients (12–17 years, $n = 395$) have been reported.⁹ In this analysis, Matsuoka and colleagues found an improvement of 22% ($P < 0.01$) of the average total combined rhinitis score (TCRS, *primary endpoint*) with 12 SQ-HDM tablets in the actively treated adolescent patients vs placebo as well as a good tolerability in this age group with a safety profile similar in the adolescent and adult subgroups of the studied population.⁹ However, clinical data from pivotal DBPC Phase III trials for children under the age of 12 years are lacking which underlines the clear (scientific and ethical) need for further exploration of SLIT with HDM tablets in this age group.

This was followed by Keisuke Masuyama and his coworkers reporting clinical study results from a multicenter (DBPC) Phase III trial of HDM SLIT tablets in 458 Japanese pediatric and adolescent patients.¹ During a run-in (baseline) period, all children had to report a minimal level of disease severity after withdrawal of antiallergic medication to qualify themselves as patients with moderate-to-severe AR. Fulfilling other inclusion criteria, the patients were then randomized 1:1 to receive active (10 000 Japanese allergy units (JAU), equivalent to 6 SQ-HDM in Europe and the United States) or placebo treatment for a treatment course of 1 year. The analysis

TABLE 1 Examples of house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet Phase II/III trials including HDM-allergic pediatric and/or adolescent patients with allergic rhinitis (modified to⁹)

Authors	Age of patients	Efficacy parameter (AR)	Treatment effect size (AR)	Editors' comments
Mosbech et al. ⁸	≥14 y	Total combined rhinitis score (TCRS), secondary endpoint	28.8% (6 SQ-HDM), $P = 0.0357$	Post hoc subgroup analysis of 489 subjects reporting AR symptoms and/or AR medication during the baseline assessment prior to randomization
Nolte et al. ⁶	≥12-85 y	TCRS, primary endpoint	17% (12 SQ-HDM), $P < 0.001$	1482 subjects enrolled
Okubo et al. ⁷	≥12-64 y	TCRS, primary endpoint	22% (10 000 Japanese allergy units [JAU]), $P < 0.001$	946 subjects enrolled
Masuyama et al. ¹	5-11 y	TCRS, primary endpoint	21%, $P = 0.002$ (10 000 JAU)	259 subjects enrolled
	12-17 y		26%, $P = 0.001$ (10 000 JAU)	199 subjects enrolled

demonstrated a treatment effect size of 21% in the pediatric (5-11 years, $n = 247$ [FAS]) and 26% in the adolescent population (12-17 years, $n = 180$ [FAS]) for the primary endpoint (TCRS) in the primary evaluation period during the last 8 weeks of treatment. As key secondary endpoint parameter, the AR symptom score was reduced by 49% in the active group and by 36.4% in the placebo group compared to baseline in this evaluation period.¹ Several other secondary endpoint parameters also underlined clinical efficacy of the treatment. Worth to mention is the fact that significant differences for both the TCRS and the AR symptom score were already demonstrated after a relative short treatment duration of only 4 weeks. In addition, *D. farinae*-specific IgG4 levels increased after a treatment course of 3 months reflecting immunological response to the treatment as no marked change was found in the placebo group. Moreover, SLIT revealed a good safety profile in both age groups.

This report of Masuyama et al. reflects the first robust randomized DBPC confirmatory (Phase III) trial to demonstrate statistically significant and clinically relevant efficacy of HDM SLIT tablets on AR in younger children in the age of 5-11 years. As such, these data are of utmost importance for the field of AIT and increase the level of evidence for this therapy as the only disease-modifying treatment option available for pediatric patients with AR. On the basis of these promising results, further trials in the same indication and age should be initiated in Europe aimed to provide an evidence-based rationale for clinicians. This would provide optimized strategies for the treatment of HDM-allergic children and adolescents in the future.

CONFLICTS OF INTEREST

Dr. Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Nuvo, grants from Circasia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from Novartis Pharma, personal fees from MEDA Pharma, grants

and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA²LEN Partner), personal fees from Pohl-Boskamp, personal fees from Indoor Biotechnologies, grants from Glaxo Smith Kline, outside the submitted work.

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