Primary prevention of asthma in high-risk children using HDM SLIT: Assessment at age 6 years

To the Editor:

Asthma has increased in recent decades worldwide, with prevalence up to 15%. In the United States, the direct cost of uncontrolled asthma is estimated at more than $300 billion during next 20 years.[1] Allergic sensitization in early life, particularly multiple sensitization, carries the greatest risk for later asthma[2] and therefore primary prevention must target infancy, before sensitization occurs. Evidence has emerged that exposure to a high dose of allergen early in life can drive the developing immune system toward a state of tolerance.[3]

One such strong immune stimulus is house dust mite (HDM), a potent, prevalent allergen. The Mite Allergy Prevention Study (MAPS) was the first trial investigating HDM sublingual immunotherapy (SLIT) for the primary prevention of atopy in nonsensitized infants.[4,5] In this proof-of-concept, double-blind, placebo-controlled study, 1 year of HDM SLIT led to a significant reduction in any sensitization compared with placebo. The treatment was safe and acceptable to families. We report the results of assessment at age 6.5 years, 5 years after cessation of immunotherapy.

The study was carried out as described in this article's Online Repository at www.jacionline.org. Briefly, 111 infants, aged 5 months and at high risk of atopy (≥2 first-degree atopic relatives) but with negative skin prick test (SPT) results, were recruited and randomized to either oral HDM or saline placebo twice daily for 12 months. At 6 years, participants underwent assessment for asthma, *a priori* primary outcome. Validated questionnaires were used for wheeze, as well as rhinitis, food allergy, and eczema. They underwent SPT to 9 allergens and an extensive respiratory assessment including spirometry with reversibility, exhaled nitric oxide, and methacholine bronchial hyperresponsiveness. This information was used to diagnose definite or likely asthma by an adjudication committee of 3 blinded, experienced, independent clinicians (for definitions, see this article's Online Repository at www.jacionline.org). An observational birth cohort "Immune Tolerance in Early Childhood" (ITEC) of high-risk infants was also recruited at the same time as MAPS. These infants were similar to the MAPS participants at baseline, and assessed identically at age 6 years. An intention-to-treat analysis was undertaken using Stata software, version 14 (StataCorp, College Station, Tex) and GraphPad Prism v7 (San Diego, Calif).

Of the 111 infants originally randomized into the study (see Fig E2 in this article's Online Repository at www.jacionline.org), 41 participants in the SLIT group (71.9%) and 44 participants in the placebo group (81.5%) completed the assessment at age 6 years. The groups were well balanced, although the placebo group had a longer duration of breast-feeding and less pet exposure at home compared with the SLIT group at baseline (see Table E1 in this article's Online Repository at www.jacionline.org). The ITEC participants were similar to the MAPS placebo group except for a shorter breast-feeding duration and younger age at baseline (see Table E2 in this article's Online Repository at www.jacionline.org).

A trend for lower rates of asthma (primary outcome) was noted in the SLIT group. For definite asthma, there was 1 case (2.9%) in the SLIT and 5 (13.5%) in the placebo groups (10.6% difference; 95% CI, 23.0% to −1.8%; $P = .11$). For likely asthma, 4 (10.8%) participants in the SLIT group and 8 (20.0%) in the placebo group were affected ($P = .27$) (Fig 1, *A*). There was no difference between the groups in lung function, fractional exhaled nitric oxide, and bronchial hyperresponsiveness (see this article's Online Repository at www.jacionline.org), or other atopic outcomes (see Table E4 in this article's Online Repository at www.jacionline.org).

In a secondary analysis, incorporating the ITEC cohort with MAPS placebo group, to increase power, significantly lower rates of definite asthma were seen in the SLIT group (1 case [2.9%]) compared with 26 [16.8%]; 13.8% difference; 95% CI, 22.0% to 5.7%; $P = .04$) (Fig 1, *B*), and a trend for less "likely asthma" was noted (13.6% difference; 95% CI, 26.2% to −2.3 %; $P = .07$). Removing from analysis, the 12 ITEC participants sensitized at baseline did not alter the results (see Table E6 in this article's Online Repository at www.jacionline.org).

For the secondary outcome of any allergic sensitization, a trend was maintained for reduced sensitization in the SLIT group compared with the placebo group ($P = .07$) (Fig 2, *A*), in a time-to-event analysis. At age 6 years, 15 (27.8%) children were sensitized in the SLIT group compared with 24 (45.4%) in the placebo group (18.2% difference; 95% CI, 35.1% to −1.8%; $P = .06$]). No difference was seen in rates of sensitization to HDM alone (Fig 2, *B*; see Table E5 in this article's Online Repository at www.jacionline.org).

We have mirrored the early food allergen exposure inducing tolerance approach with HDM for respiratory allergies. HDM allergen was selected because it is a potent immune reactor modulating the developing immune system through allergenic, endotoxin, and enzymatic effects with a bystander effect on other allergens.[6]

A recent meta-analysis on the use of allergen immunotherapy (AIT) as primary immunoprophylaxis was inconclusive.[7] This was ascribed to the limited body of evidence of the short-term effect of AIT on prevention, with no published randomized controlled trials investigating the long-term preventive effects of AIT. Previous studies have failed to demonstrate a role for the use of immunotherapy in the prevention of asthma and sensitization in young children.[8,9] However, the populations studied were older, and already sensitized to at least 1 allergen.

Our study was a small, single-center proof-of-concept study and therefore has a number of limitations. Sample size was small, and the study was only powered to assess correct ordering of sensitization. It may also have been more effective to use a larger allergen dose and longer duration of treatment, although the allergen dose used has been shown to induce immunologic response. Nonetheless, we established safety, feasibility, and preliminary proof of efficacy of SLIT in this young population.

To increase power of analysis, a comparison was made between the SLIT group and the placebo group combined with ITEC participants as additional controls. Both MAPS and ITEC participants were recruited in parallel from the same population, and the 2 cohorts were highly comparable, except breast-feeding was more frequent in the MAPS placebo group than in the ITEC cohort. Because SLIT participants were also breast-fed less than

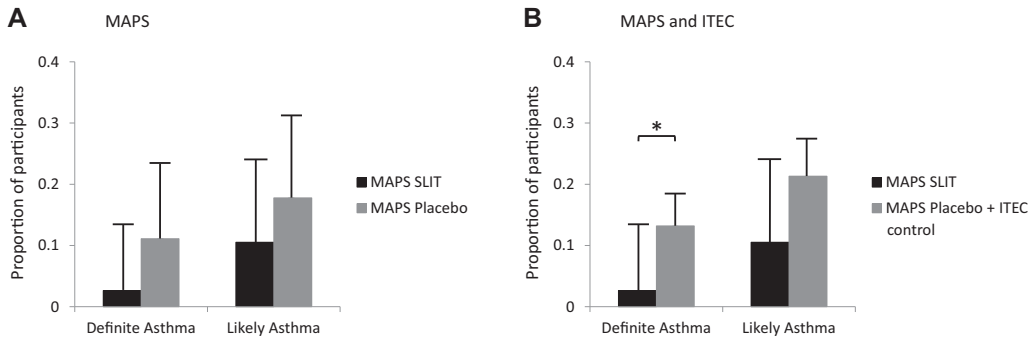

FIG 1. Comparison of definite asthma and likely asthma (definite + probable) diagnosis between (**A**) MAPS SLIT and MAPS placebo groups and (**B**) MAPS SLIT and MAPS placebo + ITEC control groups. Bars represent proportion of participants within group, with 95% CI bars. *$P < .05$.

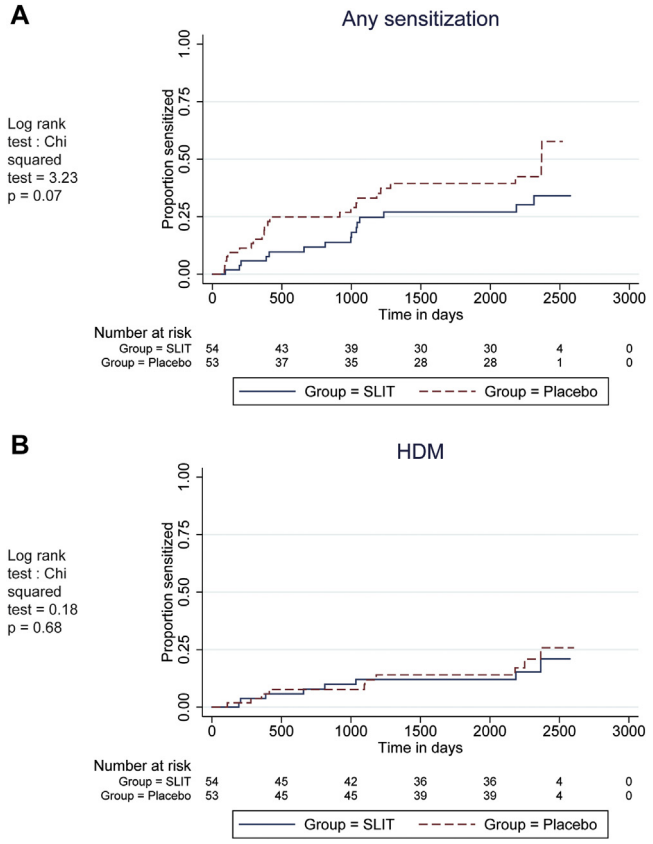

FIG 2. Kaplan-Meyer plot comparing SLIT and placebo participants' cumulative sensitization to any common allergen (**A**) or (**B**) HDM alone over the entire study follow-up period.

the MAPS placebo group, combining the MAPS placebo and ITEC cohort equalized breast-feeding rates.

In summary, this remains the only double-blind, placebo-controlled study investigating primary prevention of asthma and atopy using allergen immunotherapy, demonstrating that early-life administration of HDM SLIT may reduce childhood asthma. The results seen when the larger ITEC study is incorporated into the analysis gives credence to this conclusion. Furthermore, adequately powered studies are now required to assess the efficacy of this approach.

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Severe eosinophilic asthma with nasal polyposis: A phenotype for improved sinonasal and asthma outcomes with mepolizumab therapy

To the Editor:

Nasal polyposis (NP) is a chronic inflammatory disease of the sinuses that can cause severe nasal symptoms and systemic symptoms that include fatigue, difficulty sleeping, and impairments in social, emotional, and lifestyle well-being.[1] Patients with severe eosinophilic asthma (SEA) frequently have comorbid NP, which may impact asthma severity.[1] The anti–IL-5 mAb mepolizumab improves health-related quality of life (HRQOL) and exacerbation rates in patients with SEA[2,3]; however, its effect on HRQOL based on the presence of NP has not been examined. This letter describes results from a *post hoc* analysis of the MUSCA study[2] (n = 551; GlaxoSmithKline ID: 200862/NCT02281318) and a meta-analysis (GlaxoSmithKline ID: 208115) of MUSCA and MENSA[3] (n = 576; GSK ID: 115588/NCT01691521); their combined objective was to determine the change in HRQOL in mepolizumab-treated patients with SEA either with or without NP.

MENSA and MUSCA were phase III, placebo-controlled, randomized, double-blind, parallel-group, multicenter studies. Full study details have been published.[2,3] Briefly, patients 12 years or older with SEA (defined as asthma requiring regular treatment with high-dose inhaled corticosteroids and additional controller medication,[4] plus a blood eosinophil count ≥150 cells/μL at screening or ≥300 cells/μL in the previous year) and a history of 2 or more exacerbations requiring systemic corticosteroids in the year preceding enrollment received standard care plus mepolizumab 100 mg subcutaneously, or placebo, every 4 weeks for 32 (MENSA) or 24 (MUSCA) weeks.

In both studies, the presence of NP was determined from patients' medical records and/or external nasal examination at baseline. MUSCA assessed the mean change from baseline in the SinoNasal Outcomes Test (SNOT-22) score at the end of treatment (week 24); we analyzed this *post hoc* using mixed model repeated measures. The SNOT-22 is a 22-item patient-reported outcome tool developed for use in patients with chronic rhinosinusitis (CRS) with and without NP, assessing upper airways/nasal symptoms and HRQOL impacts of CRS; the established minimally clinically important difference (MCID) representing an improvement is an 8.9-point decrease.[5] A shared outcome of both studies was the mean change from baseline in the annual rate of clinically significant exacerbations (asthma worsening requiring systemic corticosteroids and/or hospitalization, and/or an emergency room visit). Annualized exacerbation rates were analyzed using a negative binomial regression model, and treatment differences for each study were combined using an inverse variance weighted fixed-effects meta-analysis.

For the MUSCA *post hoc* analysis, of 551 patients included in the modified intent-to-treat population, 105 (19%) had NP at baseline. Overall, 422 patients completed the SNOT-22 questionnaire at baseline (and were therefore included); 80 (19%) had NP. Mean baseline SNOT-22 scores were 43.6 ± 22.3 and 31.1 ± 20.2 for patients with and without NP. This is consistent with the reported SNOT-22 scores of patients undergoing surgery for NP and/or CRS,[5] indicating greater disease burden among patients with versus without NP. Among patients with NP, mepolizumab and placebo reduced the mean (SE) SNOT-22 score by −13.7 (2.6) and −1.9 (3.0) from baseline to week 24. The treatment difference of −11.8 (95% CI, −19.8 to −3.9) (Fig 1) exceeded the MCID, indicating a clinically meaningful improvement.[5] In patients with SEA without NP, the impact of mepolizumab was less, with a treatment difference of −4.9 (95% CI, −8.3 to −1.6). However, improvements in HRQOL related to lower airway symptoms (as measured by the SGRQ [St George's respiratory questionnaire] score) with mepolizumab were evident in both groups, with treatment differences (95% CI) of −14.6 (−21.4 to −7.7) and −6.5 (−9.6 to −3.5) in those with and without NP; these both exceeded the MCID of 4.0. This shows that mepolizumab has greater benefit in the upper and lower airways in patients with NP and SEA versus SEA alone.

For the meta-analysis of MENSA/MUSCA, of 936 patients included, 166 (18%) had NP at screening. Patients with NP had higher baseline geometric mean (SD log) eosinophil counts than did those without NP (440 [0.938] vs 290 [1.010] cells/μL). Mean baseline annual exacerbation rates were 3.1 ± 2.1 and 3.2 ± 2.3 for patients with and without NP. Mepolizumab versus placebo reduced the annual rate of clinically significant exacerbations in patients with SEA regardless of NP status, but to a greater extent in patients with NP (80%) than in without NP (49%) (Fig 2).

Overall, our results suggest that patients with SEA and comorbid NP have a higher disease burden, as reflected by the SNOT-22 and SGRQ scores, and greater systemic eosinophilic inflammation than do those with SEA but no diagnosis of NP. Furthermore, in support of other studies of biologics in SEA,[6,7] clinical improvements with mepolizumab were greater in patients with SEA and NP than in those without NP. It should be noted that in this analysis NP was identified on the basis of patients' medical records and/or external nasal examination, which may not be as reliable as performing a standardized physical examination. Nonetheless, these data suggest that patients with the clinical phenotype of SEA plus NP may have an even greater response to treatment with mepolizumab due to their morbidity. Consistent with this it is known that mepolizumab, as a systemic therapy, impacts on the upper airways, with improvement in NP size and HRQOL in patients with NP.[8] The local generation of IL-5 within the upper and lower airways in patients with SEA with NP may explain the higher circulating blood eosinophil levels compared with patients with SEA without NP.[9] Because higher blood eosinophil counts are a predictive biomarker of better response to mepolizumab in SEA,[2,3] it may not be surprising that mepolizumab has greater benefit in reducing severe exacerbations in