

Efficacy of House Dust Mite Sublingual Immunotherapy in Adults with Allergic Asthma

Edith Schussler, MD^a, and Linda S. Cox, MD^b

Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Virchow J, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA*. 2016; 315:1715-25.

BACKGROUND

Bronchial asthma is a worldwide health concern with growing prevalence.¹ Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis and allergic asthma in both children and adults.²⁻⁶ House dust mite (HDM) sensitization is present in 45% to 85 % of patients with asthma worldwide.⁷ Asthma treatment options include various pharmacotherapies (eg, inhaled bronchodilators and corticosteroids), but many patients remain symptomatic despite treatment. Allergen immunotherapy is the only treatment with a disease-modifying effect and potential for persistent benefits after completion of therapy.^{3,6} Studies have demonstrated the efficacy of treatment of HDM-stimulated allergic rhinitis and allergic asthma with subcutaneous immunotherapy to HDM allergen.^{8,9} More recent studies indicate the benefit of sublingual immunotherapy (SLIT) allergen therapy in reducing allergic symptoms to various allergens including HDM.¹⁰⁻¹³ Little has been published to date on the use of SLIT in patients with asthma. This study evaluates the efficacy of HDM SLIT in reducing asthma exacerbations in patients with HDM respiratory allergic disease not well controlled on inhaled corticosteroids (ICSs).

METHODS

This was a multicenter, randomized, double-blind, placebo-controlled trial conducted at 109 sites in 13 European countries.

^aIcahn School of Medicine at Mount Sinai, New York, NY

^bUniversity of Miami Miller School of Medicine at Holy Cross Hospital, Miami, Fla
Conflicts of interest: L.S. Cox was on the boards of American Academy of Allergy, Asthma & Immunology and American Board of Allergy and Immunology; has received consultancy fees from Stallergen Greer; and has received lecture fees from Genentech. E. Schussler declares that she has no relevant conflicts of interest. Received for publication July 5, 2016; revised November 5, 2016; accepted for publication November 9, 2016.

Available online January 18, 2017.

Corresponding author: Edith Schussler, MD, Icahn School of Medicine at Mount Sinai, 1 Gustav Levy Place, Box1089, New York, NY 10029. E-mail: edith.schussler@mssm.edu.

2213-2198

<http://dx.doi.org/10.1016/j.jaip.2016.11.032>

Patients aged 17 to 83 years with a history of at least 1 year of HDM-related rhinitis and HDM allergy—related asthma, confirmed by a positive serum specific IgE and skin prick test to HDM, who were not well controlled by ICS or combination products were included. Patients could be multiallergen sensitized, but were excluded if they had a clinical history of perennial allergic asthma or rhinitis caused by allergen other than HDM. All participants had documented reversible airway obstruction after administration of short-acting beta-agonist (SABA). Patients were excluded if they had FEV₁ less than 70% of predicted value or a hospitalization due to asthma within 3 months of randomization.

Eligible patients were randomized in a 1:1:1 randomization into 3 treatment groups: placebo tablet, 6 standard quality (SQ)-HDM SLIT tablet, or 12 SQ-HDM tablet. Inclusion criteria required that the Asthma Control Questionnaire score at randomization be between 1 and 1.5, indicating that asthma was not well controlled (score range, 0-6; values below 1, controlled asthma; values above 1.5, uncontrolled asthma). During the screening phase, which took place 5 to 7 weeks before randomization, all participants were switched from their regular ICS to budesonide and SABA. Diary records from the 2 weeks before randomization served as the participant's baseline. After randomization, during the second phase of the trial, the participants received their assigned intervention (placebo, 6 SQ-HDM, or 12 SQ-HDM tablets) in addition to ICS for 7 to 12 months. During the last 4 weeks of this intervention phase, the participants used electronic diaries twice a day to record asthma symptoms, medication use, and lung function. During phase 3, the last 6 months of the study, which started for all patients in October 2012, daily ICS use was reduced to 50% for 3 months and subsequently withdrawn completely for patients who did not experience an asthma exacerbation (as defined by the American Thoracic Society and the European Respiratory Society).

RESULTS

A total of 834 participants with HDM allergy and asthma not well controlled with ICS were randomized into the 3 groups: 6 SQ-HDM (n = 275), 12-SQ-HDM (n = 282), placebo (n = 277). The primary end point was time to first moderate or severe asthma exacerbation during the ICS reduction period.

The authors defined asthma exacerbation according to the American Thoracic Society and European Respiratory Society recommendation. Criteria for moderate asthma exacerbation included (1) nocturnal awakenings due to asthma requiring SABA use for at least 2 consecutive nights or an increase of at

TABLE I. Overview of key primary and secondary end-point efficacy results

End point	Total participants	No. (%) of participants with event	Treatment effect, HR (95% CI)	P value
Time to first exacerbation (FAS)				
Placebo group	257	83 (32)	Reference	
6-SQ-HDM group	237	62 (26)	0.69 (0.49-0.96)	.03
12-SQ-HDM group	248	59 (24)	0.66 (0.47-0.93)	.02
Time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings				
Placebo group	257	57 (22)	Reference	
6-SQ-HDM group	237	45 (19)	0.72 (0.49-1.07)	.17
12-SQ-HDM group	248	39 (16)	0.64 (0.42-0.96)	.03

FAS, Full analysis set.

least 0.75 points in daily symptom score from baseline value on at least 3 consecutive days; (2) an increase from baseline in SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day); (3) a 20% or more decrease in peak expiratory flow from baseline on at least 2 consecutive mornings or evenings or a 20% or more decrease in FEV₁ from baseline; and (4) a visit to the emergency department or an unscheduled visit to the trial site for asthma treatment not requiring systemic corticosteroids. Criteria for severe asthma exacerbation included (1) a requirement for systemic corticosteroids for the treatment of asthma symptoms for at least 3 days and (2) an emergency department visit due to asthma requiring systemic corticosteroids, or a hospitalization for more than 12 hours due to asthma.

Results revealed that both 6-SQ-HDM and 12 SQ-HDM treatment was associated with a significantly reduced risk of a moderate or severe asthma exacerbation compared with placebo (Table I). Both the 6-SQ-HDM and the 12-SQ-HDM tablets were found to be equally superior to placebo, showing an approximate 10% reduction in asthma exacerbations, primarily driven by moderate exacerbations, at 6 months for both the 6- and 12-SQ doses. There was no additional benefit in the higher dose group with regard to this primary outcome measure.

Secondary outcomes were deterioration in asthma symptoms, change in allergen specific IgG₄, change in asthma control or asthma quality-of-life questionnaires, and adverse events. Compared with the placebo group, the 12 SQ-HDM group (Table I) demonstrated reduced risks of (a) moderate asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings, (b) moderate asthma exacerbation with deterioration in lung function, and (c) moderate asthma exacerbation with increased SABA use. For the 6 SQ-HDM group, only time to first asthma exacerbation with deterioration in lung function was statistically significant from placebo. There was a significant and dose-dependent increase in IgG₄ levels in both treatment groups compared with the placebo group. Of note, there was no difference for change in the Asthma Control Questionnaire score or the asthma study of life questionnaire score for either dose. Adverse events occurred in 72% of participants in a dose-dependent manner, with all adverse events being mild (most commonly moderate oral pruritus, mouth edema, or throat irritation), with no severe systemic allergic reactions reported.

The authors concluded that among adults with HDM allergy-related asthma not well controlled by ICS, the addition of

once-daily HDM SLIT tablet significantly prolonged the time to first asthma exacerbation during the ICS reduction.

CRITICAL APPRAISAL

This was a well-designed randomized placebo-controlled trial focusing on adult patients with HDM-triggered asthma with inadequate symptom control despite inhaled corticosteroid. There were some significant limitations to this trial including the exclusion of patients with more severe or unstable asthma and patients younger than 18 years. Although approximately two-third of participants were polysensitized, those with a relevant clinical history of perennial allergic asthma or rhinitis caused by other allergens were excluded. This significantly limits the population to which these results apply. In addition, though this trial focuses on allergic asthma, no mention was made of the inclusion or exclusion of relevant allergy medications. Also, in the reporting of adverse events, the authors did not comment on oral itch or the risk of unblinding due to this symptom with active intervention.

The overall results indicate a significant reduction in risk for asthma exacerbation in the treatment group versus the placebo group (~10% at 6 months). However, the quality-of-life questionnaires did not reflect these changes, a result that could significantly affect outcomes in clinical practice. SLIT is a daily medication taken at home and lack of perceived benefit may have adverse effects on adherence.

The full benefit of SLIT may be underestimated by these studies in which the treatment length of 6 months may be too short to realize the full benefits of SLIT, which is typically continued for 3 to 4 years. With longer treatment, both patient perception and actual benefit of treatment may increase. In addition, the power calculation for this study was based on the assumption that 65% of participants in the placebo group would experience an asthma exacerbation, with a reduction in hazard rate time to first asthma exacerbation of approximately 30% corresponding to a hazard ratio (HR) of 0.70 considered clinically relevant. The actual rate of exacerbations in the placebo group was about half that expected.

RECOMMENDATIONS

Overall, the results indicate that the addition of 6 or 12 SQ-HDM SLIT to maintenance medications may have beneficial effects in adult patients with HDM-triggered asthma. The addition of this treatment is expected to reduce the risk of asthma

exacerbation by about 10% at 6 months, and should be considered in adult patients with HDM-allergy-related asthma not well controlled with ICS.

REFERENCES

1. Boulet LP, FitzGerald JM, Reddel HK. The revised 2014 GINA strategy report: opportunities for change. *Curr Opin Pulm Med* 2015;21:1-7.
2. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127:S1-S55.
3. Bousquet J, Maasch H, Martinot B, Hejjaoui A, Wahl R, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids, II: comparison between parameters assessing the efficacy of immunotherapy. *J Allergy Clin Immunol* 1988;82:439-46.
4. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995;151:969-74.
5. Polosa R, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. *Allergy* 2004;59:1224-8.
6. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007;62:943-8.
7. Dust mite allergens and asthma—a worldwide problem. *J Allergy Clin Immunol* 1989;83:416-27.
8. Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. *J Allergy Clin Immunol* 2013;132:1322-36.
9. Eifan AO, Calderon MA, Durham SR. Allergen immunotherapy for house dust mite: clinical efficacy and immunological mechanisms in allergic rhinitis and asthma. *Expert Opin Biol Ther* 2013;13:1543-56.
10. Dahl R, Roberts G, de Blic J, Canonica GW, Kleine-Tebbe J, Nolte H, et al. SQ grass sublingual allergy immunotherapy tablet for disease-modifying treatment of grass pollen allergic rhinoconjunctivitis. *Allergy Asthma Proc* 2016;37:92-104.
11. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717-725.e5.
12. Soh JY, Thalayasingam M, Ong S, Loo EX, Shek LP, Chao SS. Sublingual immunotherapy in patients with house dust mite allergic rhinitis: prospective study of clinical outcomes over a two-year period. *J Laryngol Otol* 2016;130:272-7.
13. Yuta A, Ogawa Y, Suzuki Y, Arikata M, Kozaki H, Shimizu T, et al. Clinical efficacy of sublingual immunotherapy for Japanese cedar pollinosis in the first follow-up year [in Japanese]. *Arerugi* 2015;64:1323-33.

Reproduced with permission of copyright owner.
Further reproduction prohibited without
permission.