had a higher proportion of symptom-free days than daily INCS users. This provides support for the suggestion that there may be a role for on-demand INCS among children with allergic rhinoconjunctivitis. Further research into this dosing strategy should be done, perhaps with a greater diversity of allergic rhinoconjunctivitis triggers.

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Joan H. Dunlop, MD
Corinne A. Keet, MD
Baltimore, MD

Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial

Virchow JC, Backer V, Kuna P, et al. *JAMA*. 2016;315(16): 1715–1725

PURPOSE OF THE STUDY. To evaluate the efficacy and adverse events of 2 doses of house dust mite (HDM) sublingual allergen immunotherapy (SLIT) versus a placebo for asthma exacerbations during inhaled corticosteroid (ICS) reduction in cases of unstable asthma.

STUDY POPULATION. A total of 834 subjects (99% white, mean age of 33 years [range of 17–83 years], 48% women) were randomized 1:1:1 to receive 2 HDM tablet doses or a placebo. Six hundred ninety-three participants completed the trial. Dropout rates were similar among the 3 treatment groups.

METHODS. This was a double-blind, placebo-controlled, randomized trial comparing HDM SLIT using daily tablets in 2 doses (6 SQ-HDM or 12 SQ-HDM) with using a matching placebo. All subjects had HDM-related asthma and allergic rhinitis for >1 year, a positive skin prick test to HDM, and detectable HDM-specific serum IgE. All subjects had partly controlled (72%) or uncontrolled (28%) asthma (per a prespecified GINA algorithm) on ICS (400–1200 mcg budesonide equivalent) at inclusion. At randomization, 1 of the 3 study treatments was added for 7–12 months depending on the date of entry. During the last 6 months of the treatment period, the daily ICS dose was reduced by 50% for 3 months and subsequently withdrawn from the subjects who did not experience an asthma exacerbation. The primary end point, the time to the first moderate or severe asthma exacerbation, was measured from the start of the ICS reduction period until the first exacerbation. Secondary end points included asthma quality of life measurements and adverse events.

RESULTS. Both doses of HDM SLIT tablets significantly reduced the risk of a moderate or severe asthma exacerbation compared with the placebo (hazard ratio [HR] 0.72 for the 6 SQ-HDM group [95% CI, 0.52–0.99], $P = .045$; and HR 0.69 for the 12 HDM-SQ group [95% CI, 0.50–0.96], $P = .03$). There was no significant difference between the 2 active-treatment groups (HR 0.96; $P = .84$). The absolute risk for the first asthma exacerbation was 26% ($n = 62$) for the 6 SQ-HDM group, 24% ($n = 59$) for the 12 SQ-HDM group, and 32% ($n = 83$) for the placebo group, primarily involving moderate rather than severe exacerbations and with no significant difference between the 2 active-treatment groups. There was no significant difference in the change in quality of life for either active-treatment group. Local treatment-related adverse events were common in both active-treatment doses. There were no reports of anaphylaxis.

CONCLUSIONS. This is the first published controlled trial to show that patients with HDM-related asthma whose symptoms were not well controlled with ICS can achieve significant improvement in asthma control with HDM SLIT during ICS reduction. The absolute reduction after 6 months of treatment was 10%, primarily due to an effect on moderate exacerbations.

REVIEWER COMMENTS. This is a unique study showing that HDM SLIT is associated with a modest reduction in asthma exacerbations in adult patients with poorly controlled HDM-related asthma, even with ICS reduction. In March 2017, HDM SLIT tablets were approved by the FDA for use for AR in the United States by patients ages 18–65 years. In the European Union, HDM SLIT tablets are approved for use in children.

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Alan Goldsobel, MD
San Jose, CA

Treatment Effect of Sublingual Immunotherapy Tablets and Pharmacotherapies for Seasonal and Perennial Allergic Rhinitis: Pooled Analyses

Durham SR, Creticos PS, Nelson HS, et al. *J Allergy Clin Immunol*. 2016;138(4):1081–1088.e4

PURPOSE OF THE STUDY. To indirectly compare the effect of sublingual immunotherapy tablets (SLIT) with selected pharmacotherapies versus placebo on nasal symptom scores in perennial (PAR) and seasonal allergic rhinitis (SAR).

STUDY POPULATION. Twenty-three SAR trials and 11 PAR trials with 18 914 patients were included in the analysis. Subjects enrolled in the trials ranged from 5 to 85 years of age.

METHODS. The authors pooled analyses from randomized, double-blind, placebo-controlled trials of SLIT to timothy grass, short ragweed, and house dust mite (HDM) and pharmacologic treatments with montelukast, desloratadine, and mometasone furoate nasal spray (MFNS). Unpublished ad hoc data on file with the manufacturers were also used. Total nasal symptoms scores (TNSS) with treatment were compared with placebo.

RESULTS. Relative to placebo, TNSS improvements in the grass SAR trials ranged from 4.0% to 27.2% (overall

16.3% improvement as compared with placebo). In the 2 ragweed SLIT studies, overall improvement relative to placebo was 17.1%. These treatment effects were numerically greater than those for montelukast (0.65% to 10.3%, overall 5.4% improvement compared with placebo) and desloratadine (1.7% to 12.5%, overall 8.5% improvement compared with placebo). In contrast, MFNS had a numerically greater effect than did SLIT (13.1% to 28.1%, overall 22.2% improvement compared with placebo). In 2 studies of HDM SLIT for PAR, overall TNSS improvement was 16.1% higher than with placebo. This effect was greater than that seen for montelukast, desloratadine, and MFNS (3.7%, 4.8%, and 11.2% improvement compared with placebo, respectively).

CONCLUSIONS. As compared with placebo, grass and ragweed SLIT are more effective at lowering TNSS than montelukast and desloratadine but somewhat less effective than MFNS. HDM SLIT had a greater effect on TNSS than the pharmacologic treatments.

REVIEWER COMMENTS. Currently, the FDA has approved SLIT tablets for grass and house dust mite allergies. The currently available preparations are very expensive and often not covered by insurance. A great weakness in the study and marketing of new products is that they are usually not compared with existing products in head-to-head studies. Subcutaneous allergen immunotherapy (SCIT) has been proven effective (and more effective than pharmacotherapy) for numerous (but not all) aeroallergens. SLIT tablet doses are not easily compared with SCIT doses, but data indicate that significantly higher monthly doses of SLIT than SCIT are necessary for efficacy. At this point, if a patient has isolated allergies to grass, ragweed, or dust mites, SLIT tablets are an option, but cost and other factors (such as the potential for long-lasting therapeutic benefit with SLIT) must be considered in the discussion between patients and their allergists.

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Mitchell R. Lester, MD
Norwalk, CT

Asthma

PATHOPHYSIOLOGY, DIAGNOSIS, AND MANAGEMENT

Early Life Rhinovirus Wheezing, Allergic Sensitization, and Asthma Risk at Adolescence

Rubner FJ, Jackson DJ, Evans MD, et al. *J Allergy Clin Immunol*. 2017;129(2):501–507

PURPOSE OF THE STUDY. To define the relationships among specific viral illnesses and the type and timing of aeroallergen sensitization with the persistence of asthma into adolescence.

STUDY POPULATION. This is a prospective cohort study that enrolled 289 newborns who had a parental history of respiratory allergies and/or asthma and were followed to age 13 years (n = 213).

METHODS. After enrollment, the infants had scheduled visits at ages 2, 4, 6, 9, and 12 months and annually thereafter. They were also seen during periods of acute illness. At these visits, nasal lavage was collected and analyzed for respiratory viruses. The viral panel included RSV, RV, influenza types A and B, parainfluenza virus types 1 to 4, adenovirus, coronavirus, and enterovirus. Allergen-specific IgE levels were determined at ages 1, 2, and 3 years for *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, *Alternaria alternata*, and dog and cat allergens and were repeated at ages 5, 6, 9, 11, and 13 years with the addition of ragweed, silver birch, timothy grass, and cockroach. Wheezing during the first 3 years of life and asthma during school age were determined by physician diagnosis, the use of β agonists, daily asthma controller medications, or the use of oral steroids for exacerbation.

RESULTS. A total of 454 wheezing illnesses were documented during the first 3 years of life. Viruses detected included the following: RV (48%), RSV (21%), parainfluenza viruses (12%), metapneumovirus (7%), coronaviruses (5%), adenovirus (4%), influenza types A and B (4%), and enteroviruses (2%). RSV-induced wheezing accounted for an increased risk of asthma during school ages 6, 8, and 11 years; however, the association was lost by age 13 years. On the other hand, RV-associated wheezing during early childhood was associated with asthma that persisted to age 13 years (OR +3.3; 95% CI, 1.5–7.1). Additionally, 65% of children who were sensitized by age 1 year had asthma that persisted to age 13 years; children who were not sensitized by 1 year of age but were sensitized by age 5 years had a 40% rate of asthma in adolescence, and the remaining children who were not sensitized by age 5 years had an asthma rate of 17%. Subsequently, those with both early-life, RV-associated wheezing and aeroallergen sensitization by age 3 years had the highest risk of persistent asthma. Protective factors that reduced asthma risk at age 13 years included the presence of a cat in the home at the time of birth, while the protective impact of a dog in the home waned by age 13 years.

CONCLUSIONS. This study found that high-risk children with a parental history of allergies and/or asthma were more likely to develop asthma that persisted into adolescence when they had RV and aeroallergen sensitization in early childhood.

REVIEWER COMMENTS. This study highlights that the timing of wheezing illness, the type of viral infection causing the illness, and aeroallergen sensitization are all important influences on the development of persistent asthma. This study demonstrated that RV-associated wheezing correlates with longer-lasting asthma than RSV-associated wheezing in

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Mitchell R. Lester

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