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

BACKGROUND

- Treatment options for patients with house dust mite (HDM) allergic disease include inhaled corticosteroids and long acting beta agonists, but up to 30% of patients remain symptomatic, uncontrolled, or both despite treatment.
- Allergen immunotherapy is the only treatment option for allergic disease with evidence of a disease-modifying effect and thus a potential for sustained benefits when therapy is terminated.

OBJECTIVE

- To evaluate the efficacy of the HDM sublingual immunotherapy tablet in 2 different doses (6 SQ-HDM and 12 SQ-HDM) vs placebo, measured by reducing the risk for an asthma exacerbation during a 6-month inhaled corticosteroid reduction period.

METHODS

- **Design**: double-blind, randomized, parallel, placebo-controlled trial; Duration: 18 months
- **Inclusion Criteria:** adult with a positive result for the HDM-specific serum immunoglobulin E (IgE) and skin prick test; clinical history of more than one year of allergic asthma and allergic rhinitis with HDM being considered clinically as a major trigger, not well controlled by inhaled corticosteroid (equivalent to budesonide 400-1200mcg); FEV1 at randomization of 70% or more of predicted value; asthma control questionnaire (ACQ) score from 1 to 1.5
- **Exclusion Criteria:** hospitalization due to an asthma exacerbation within 3 months prior to randomization; relevant clinical history of perennial allergic asthma or rhinitis caused by other allergens
- **Primary Outcome Measure:** Time to first moderate or severe asthma exacerbation during the inhaled corticosteroid reduction period
- **Secondary Outcome Measure:** Deterioration in asthma symptoms and nocturnal awakenings; change in allergen-specific immunoglobulin G4 (IgG4) from baseline; change in asthma control or asthma quality of life questionnaires and adverse events; proportion of participants with a minimal important difference in ACQ or standardized Asthma Quality of Life Questionnaire (AQLQ) score without an increased dose of ICS, or with no minimal important difference in ACQ or AQLQ score despite lower inhaled corticosteroid usage at the end of trial
- 834 patients received either placebo, 6 SQ-HDM sublingual immunotherapy tablet, or 12 SQ-HDM sublingual immunotherapy tablet
- Power was 80% to detect a difference between HDM sublingual immunotherapy tablet and placebo in the time to first asthma exacerbation corresponding to a hazard ratio of 0.70 at the 5% significance level. This was calculated to be sufficient for 240 people per group
- Data handling method was intent-to-treat

RESULTS

- 742 of the 834 randomized patients completed the trial
- **Primary Outcome Measure:** The two treatment groups, 6SQ-HDM and 12SQ-HDM, had significantly reduced risk of a moderate or severe asthma exacerbation compared with placebo

(HR 0.72 [95% CI, 0.52-0.99] for the 6SQ-HDM group and HR 0.69 [95% CI, 0.50-0.96] for the 12SQ-HDM group).

- **Secondary Outcome Measures:** The time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings was only found to be statistically significant in the 12SQ-HDM group (p=0.03). There was no statistically significant difference between active treatment and placebo in ACQ or AQLQ score without an increased dose of inhaled corticosteroid.
- **Author's Conclusion:** The addition of HDM sublingual immunotherapy to maintenance medications improved time to first moderate or severe asthma exacerbation during inhaled corticosteroid reduction, with estimated absolute reduction at 6 months of 9-10%.

STRENGTHS

- Participants randomized to placebo, 6SQ-HDM group, or 12SQ-HDM
- Gold standard design study used (double-blind, placebo controlled trial)
- Intent to treat data analyses
- 80% power

LIMITATIONS

- Large range of 7 to 12 months for period 2
- Manufacturer of HDM sublingual immunotherapy tablet was also the study sponsor
- Lack of adverse event statistical analysis
- Lack of ethnic diversity in study participants
- Possible unblinding due to adverse events

CONCLUSION

- The study showed a statistically significant reduction in time to first asthma exacerbation with HDM sublingual immunotherapy; however, the clinical usefulness of the data is exaggerated by the authors.
    - The reduction was primarily due to an effect on moderate exacerbations even though both moderate and severe exacerbations were analyzed.
    - Compliance may decrease for this medication since it must be administered daily and only provides a 9-10% reduction in first exacerbation at 6 months.
    - The more severe adverse effects of this medication barely discussed by the authors could decrease the acceptance by physicians in clinical practice.
- Future research:
    - The pediatric population also suffers from HDM allergen induced asthma; therefore, a trial studying the usefulness in pediatric patients should be conducted.
    - Due to the fact allergen immunotherapy has evidence of a disease modifying effect, a study with a universal length for period 2 looking at long term efficacy even after stopping therapy is warranted.

Reference: Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, Ljørring C, Riis B, de Blay F. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA. 2016. Apr 26;315(16):1715-25.

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