Efficacy of House Dust Mite Sublingual Tablet in the Treatment of Allergic Rhinoconjunctivitis: A Randomized Trial in a Pediatric Population
Okamoto Y, Fujieda S, Okano M, Hida H, Kakudo S, Masuyama K. Pediatr Allergy Immunol. 2019;30(1):66–73

PURPOSE OF THE STUDY: To investigate the efficacy, safety, and immunologic response of standardized sublingual house dust mite (HDM) tablets in Japanese pediatric patients.

STUDY POPULATION: Included in the study were patients ≥5 and ≤16 years of age with allergic rhinitis symptoms for ≥2 years, a score of ≥3 on quantitative analysis of specific immunoglobulin E antibodies to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* antigens, positive nasal provocation test result for HDM, and Rhinitis Total Symptom Score ≥6 points per day for 7 days before randomization. Those with symptoms from other allergens, mild persistent or more-severe asthma, or inhaled corticosteroid use were excluded.

METHODS: This multicenter, double-blind, randomized placebo-controlled trial was conducted at 51 Japanese medical institutions from October 2015 to December 2016. Subjects were randomly assigned 1:1 to placebo or HDM tablets with an index of reactivity of 300 daily for 52 weeks. Symptoms and rescue medication use were recorded daily in a patient diary. The primary end point was the average adjusted symptom score for week 48 to 52, derived from daily Rhinitis Total Symptom Scores and adjusted for rescue medication use.

RESULTS: Of 438 patients who were randomly assigned, 193 patients in the treatment group and 210 patients in the placebo group completed the study. The average adjusted symptom score was significantly lower in the treatment group compared with placebo (6.32 vs 7.27, *P* = .0005), with a least-squares mean difference of −13.1%. Improvement was seen at weeks 8 to 10 and was maintained throughout. Nasal Individual Symptom Scores were significantly lower in the treatment group, whereas Average Rescue Medication Scores and Ocular Individual Symptom Scores were not. Specific immunoglobulin E antibodies to HDM nearly doubled, whereas specific immunoglobulin G4 antibodies approximately tripled in the treatment group. Mild or moderate adverse events (oral pruritus, mouth edema, throat irritation, ear pruritus, and mouth swelling) occurred in most patients (96.8% of treated patients, 94.5% of placebo patients), typically from days 1 to 14. Two serious adverse events were reported in the placebo group and 6 were reported in the treatment group, leading to drug discontinuation in 1 patient with pseudocroup. Overall, 8% of randomly assigned patients discontinued the study, mostly because of adverse effects. There were no deaths or anaphylactic events requiring intramuscular epinephrine.

CONCLUSIONS: This study demonstrates efficacy and safety of HDM sublingual tablets in pediatric patients with perennial allergic rhinitis due to HDM allergy. Treatment conferred significant and sustained improvement in symptom scores, with a similar immunologic response and safety profile, as previously shown in older age groups.

REVIEWER COMMENTS: This study is limited by a lack of objective outcomes, such as peak nasal inspiratory flow or nasal provocation tests. The investigators also excluded patients with persistent asthma and symptomatic rhinitis due to other allergens, which commonly occur in patients with HDM-triggered rhinitis. Although modest improvement in symptoms was shown, daily therapy over a 52-week treatment course may be impractical for pediatric patients. One likely goal of HDM immunotherapy may be to decrease use of other medications, but this was not seen in the current study. Further studies are needed in this population to assess optimal treatment duration and whether treatment confers sustained benefit after drug discontinuation.

ALLERGIC SKIN DISEASES

The Nonlesional Skin Surface Distinguishes Atopic Dermatitis With Food Allergy as a Unique Endotype
Leung DYM, Calatroni A, Zaramela LS, et al. Sci Transl Med. 2019;11(480):eaav2685

PURPOSE OF THE STUDY: To determine if children with atopic dermatitis and food allergy (AD FA+) to peanut have skin features that distinguish them from children with atopic dermatitis without food allergy (AD FA−) and nonatopic (NA) controls.

STUDY POPULATION: Sixty-two children with atopic dermatitis (AD) of any severity between the ages of 4 to 17 years were recruited to National Jewish Health. The 3 groups consisted of 21 children with food allergy (AD FA+) to at least peanut, 19 without food allergy (AD FA−), and 22 NA controls. Groups were balanced for age, sex, and race and were reported to have similar AD severity.

METHODS: This was a prospective, clinical mechanistic study to evaluate for differences among the AD FA+, AD FA−, and NA groups. They used skin tape stripping (STS) of lesional and nonlesional skin to examine transdermal water loss (TEWL) and stratum corneum composition. The primary outcome was TEWL area under the curve measured before STS and after 5, 10, 15, and 20 skin tape tests. This was combined with the use of proteomics, lipidomics, electron microscopy, and transcriptomics to evaluate STS samples. In addition, the microbiome was assessed by skin swabs.
RESULTS: TEWL area under the curve assessed on nonlesional skin demonstrated that subjects with AD FA+ had a significant increase in TEWL when compared with subjects with AD FA− and NA controls. There was noted to be significantly higher amounts of filaggrin (FLG) breakdown products at skin tape tests 15 and 16 in the NA group when compared with subjects with AD FA− and AD FA+, with the AD FA+ group demonstrating the lowest amount of FLG breakdown products. They mapped shotgun metagenomics microbial sequence reads and found an increased relative abundance of Staphylococcus and Micrococcus in subjects with AD FA+ compared with NAs on nonlesional skin. In addition KRT5, KRT14 (basal markers), and KRT16 (marker of hyperproliferation) at skin tape tests 15 and 16 were all increased in the AD FA+ group compared with subjects with AD FA− and NA, suggesting poor terminal differentiation of proliferating keratinocytes. Through transcriptome analysis of STS, they found that patients with AD FA+ had more dendritic cell and Th2 immune activation signatures in nonlesional skin. These differences were found to be independent of AD severity because there were no differences in AD severity among the 2 groups with AD, measured by Scoring Atopic Dermatitis, Eczema Area and Severity Index, and Nottingham Eczema Severity Score. In addition, network analysis demonstrated that these keratins (KRT5, KRT 14, and KRT 16) were positively correlated with AD FA+ and that FLG breakdown products were negatively correlated with AD FA+.

CONCLUSIONS: Increased TEWL, low amounts of FLG breakdown products, and increased keratin proteins in the nonlesional skin of the AD FA+ group all suggest that in children with AD FA+, skin exhibits abnormal barrier function and lack of epidermal terminal differentiation.

REVIEWER COMMENTS: The authors demonstrate that both AD and food allergy affect the structure of nonlesional skin at the stratum corneum. This highlights that nonlesional skin abnormalities not visible to the eye may exist in our patients with both disorders. Further insights into these differences could help to improve treatment of AD and perhaps even prevent food allergy.

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Antibiotic Choice and Methicillin-Resistant Staphylococcus aureus Rate in Children Hospitalized for Atopic Dermatitis

Wang V, Keefer M, Ong PY. Ann Allergy Asthma Immunol. 2019;122(3):314–317

PURPOSE OF THE STUDY: To examine the prescribing patterns of systemic antibiotics for children hospitalized for atopic dermatitis (AD) exacerbation compared with infectious complications.

STUDY POPULATION: A total of 174 patients with AD who were admitted to Children’s Hospital Los Angeles from 2013 to 2018 were included (70 with AD exacerbation and 104 with infectious complications).

METHODS: Subjects were identified via retrospective chart review by International Classification of Diseases, Ninth Revision and International Classification of Diseases, 10th Revision codes for AD. Secondary codes for contact dermatitis and other eczema, dermatitis unspecified, and unspecified contact dermatitis, unspecified cause were only included in patients with a physician diagnosis of AD. Infectious complications of AD included patients experiencing focal infections (cellulitis or abscess), invasive infections (bacteremia, osteomyelitis, septic arthritis, or endocarditis), or eczema herpeticum, whereas acute exacerbation of AD was confirmed in the history of present illness, physical examination, or diagnosis on physician discharge summary.

RESULTS: Systemic antibiotics were administered in 80% (56 out of 70) of patients with AD exacerbation and 94% (98 out of 104) of those with infectious complications. The most frequently prescribed antibiotics on admission offered empirical coverage against methicillin-resistant Staphylococcus aureus (MRSA), specifically clindamycin and vancomycin, at a total rate of 88% for both AD exacerbation and infectious complications. Rates of use were similar between both groups (75% and 74% for clindamycin and 13% and 14% for vancomycin, in AD versus infectious groups, respectively). Anti-MRSA agents were prescribed at discharge at similar rates between both groups; clindamycin was most commonly prescribed (54% of AD patients and 59% of patients with infectious complications). Sulfamethoxazole-trimethoprim was also prescribed a similar rates for both groups (4% AD, 5% infectious). MRSA was significantly less common in children with AD exacerbation (22%) versus infectious complications (39%) on wound culture results. Significant differences in patients with infections complications included longer length of stay ($P < .0001$) and higher C-reactive protein levels and erythrocyte sedimentation rates ($P = .007$ and $P = .003$, respectively). Patients with AD exacerbation had higher total serum immunoglobulin E levels, but the difference was not significant ($P = .07$).

CONCLUSIONS: Although AD is a risk factor for $S$ aureus infections, distinguishing clinical characteristics between AD exacerbation and infectious complications is challenging, and no standard definition for secondary infection or superinfection of AD exists. Antibiotic use for AD exacerbation varies, but empirical use of anti-MRSA agents may not be appropriate. C-reactive protein or erythrocyte sedimentation rate may have a role in distinguishing patients with infectious complications from those with exacerbation.
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