ALLergy) recommend the consideration of montelukast therapy for this population, this study suggests otherwise. What is of interest is the phenotypic differentiation made in this wheezy infant population between children with episodic viral and chronic wheeze who exhibit breakthrough symptoms between exacerbations. This characterization is intriguing and further discussion of whether to distinguish this preschool wheezing population based on subgroups could assist in practice and management.

Mepolizumab for Severe Eosinophilic Asthma (DREAM): A Multicentre, Double-Blind, Placebo-Controlled Trial

PURPOSE OF THE STUDY. To elucidate the efficacy, safety, and patient characteristics of responsiveness to mepolizumab (a humanized monoclonal antibody against interleukin 5). Previous small, proof-of-concept studies in subjects with severe, eosinophilic asthma revealed that mepolizumab decreased exacerbation rates.

STUDY POPULATION. From 81 multinational centers, 621 patients were enrolled. Major inclusion criteria included: age 12 to 74 years, asthma diagnosis with objective measures, ≥2 asthma exacerbations requiring oral corticosteroids in the last year, refractory asthma as defined by the American Thoracic Society criteria, and signs of eosinophilic inflammation (sputum eosinophil count ≥3%, an exhaled nitric oxide concentration ≥50 ppb, peripheral blood eosinophil count ≥0.3 × 10⁹/L, or prompt deterioration of asthma control with inhaled or oral steroid weaning). Smokers, present or former (≥10 pack-years), were excluded.

METHODS. Subjects were randomized to receive placebo or 1 of 3 doses of mepolizumab (75, 250, or 750 mg). Every 4 weeks for 13 cycles, patients received infusions. Asthma symptom scores, objective lung testing results, and blood eosinophil counts were collected at baseline and follow-up visits. The primary outcome of verified, clinically significant exacerbations during treatment and 4 weeks thereafter was defined a priori.

RESULTS. All mepolizumab-treated groups demonstrated a significant decrease in clinically significant exacerbations (75 mg: −48% [P < .0001]; 250 mg: −39% [P = .005]; 750 mg: −52% [P < .0001]). Visits to emergency departments and admissions also decreased; however, no significant changes in spirometry or asthma control scores were noted. No treatment-associated deaths occurred, and other potential adverse events were equivocal in the placebo and treatment groups.

CONCLUSIONS. Mepolizumab is generally safe and reduces exacerbation rates in select patients with asthma who have the severe, refractory, eosinophilic subtype.

REVIEWER COMMENTS. Using more clinically available inclusion criteria and a larger cohort, mepolizumab provides another tool in select patients with severe, eosinophilic asthma. The study supports the clinical importance of asthma phenotyping in effectively treating asthma subjects but provides no insight for efficacy in other asthma phenotypes. The equivalent responses from the 75- and 750-mg dose might improve the cost to benefit ratio of mepolizumab depending on the manufacturer’s pricing strategy. Despite seemingly optimized design and execution, all results must be viewed through a scrutinizing lens because the manufacturer participated in all aspects ranging from design to writing.

IMMUNOTHERAPY
Efficacy of Subcutaneous and Sublingual Immunotherapy With Grass Allergens for Seasonal Allergic Rhinitis: A Meta-Analysis-Based Comparison

PURPOSE OF THE STUDY. To compare the efficacy of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) to grass by meta-analysis of double-blind, placebo-controlled trials.

STUDY POPULATION. Among 36 studies selected for this meta-analysis, 14 included children.

METHODS. An electronic literature search identified 36 randomized controlled trials (RCTs) comparing SCIT and SLIT to placebo for grass pollinosis. All the studies assessed symptom scores and 31 assessed medication scores as outcome measures. To standardized comparative studies, the authors used the “standard mean difference” method (SMD) to compare SCIT or SLIT versus placebo. A “fail-safe” number (the number of insignificant or missing studies that would need to be added to a meta-analysis to reduce a significant result to insignificance) calculation was performed.

RESULTS. The 36 RCTs (22 SLIT [10 drops, 12 tablets], 14 SCIT) included 3014 treated patients and 2768 patients given placebo. Nine SLIT studies and 5 SCIT studies included children. There was great variation in the
number of subjects enrolled (15–943) and the duration of treatment (1.5–36.0 months). All RCTs of SLIT showed improved symptom scores as compared with placebo, but only 3 of 10 studies using SLIT drops, 8 of 12 using SLIT tablets, and 12 of 14 using SCIT reached statistical significance. The SMDs indicated a significant and considerable benefit from SCIT and mild-moderate benefit from SLIT. The fail-safe number for symptom scores was 530 for SLIT and 232 for SCIT studies. Medication scores were obtained in 20 SLIT and 11 SCIT RCTs. The pooled data for the SCIT and SLIT studies showed significant reduction in SMD of symptoms scores (SLIT drops: −0.37, SLIT tablets: −0.30, SCIT: −0.58). However, only ~50% of the studies of each method showed a statistically significant reduction in medication score as compared with placebo. The fail-safe number for medication scores was 384 for SLIT and 66 for SCIT studies. There were 0.86 adverse events/patient reported for patients receiving SCIT and 2.13 adverse events/patient reported in those receiving SLIT. A “robust analysis” done by eliminating each study from the total group did not change the results, indicating that no one study was solely responsible for the findings.

CONCLUSIONS. In patients with grass-induced seasonal allergic rhinoconjunctivitis, SCIT is more effective than SLIT in reducing symptoms and the need for rescue medication.

REVIEWER COMMENTS. SLIT is an area of recent intense research and potentially an attractive alternative to SCIT for children. For a small handful of allergens, SLIT has been shown to be more effective than placebo when given in much higher total monthly doses than are given by SCIT. But, we do not treat our patients with placebo. We treat them with approved materials. The high-dose materials used in those European studies are not approved in the United States. Low-dose SLIT (as is available) has not been shown to be more effective than placebo. In SCIT, numerous allergens are given at the same time with time-proven efficacy. The results of a limited number of studies using SLIT to numerous allergens given at once are not impressive. Until high-dose SLIT has been proven superior to SCIT, it should not be practiced.

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Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma: A Systematic Review

PURPOSE OF THE STUDY. This was a systematic review of the clinical efficacy and safety of sublingual immunotherapy (SLIT) delivered via an aqueous solution. This publication was derived from a Comparative Effectiveness Review by the same authors, commissioned by the U.S. Agency for Healthcare Research and Quality.

STUDY POPULATION. Sixty-three randomized controlled trials (RCTs) involving 5131 participants met the inclusion criteria and were included in this systematic review. Ages ranged from 4 to 74 years. Most of the studies were trials of grass and dust mite SLIT. Also included were trials of tree, ragweed, cat, and Alternaria SLIT. All but one of the trials in this report used a single allergen extract for treatment. All of the included studies were required to enroll patients with confirmed allergic rhinoconjunctivitis or allergic asthma with skin or specific immunoglobulin E blood testing. Diagnosis of asthma was required to be by objective criteria (pulmonary function testing) or according to established guidelines.

METHODS. Multiple databases were searched for the period 1950 to December 22, 2012, for English-language RCTs on the effects of SLIT for allergic rhinoconjunctivitis or allergic asthma. Only studies using allergen formulations available in the United States were included. No trials of sublingual tablets were included. The extremely variability of the published RCTs in dosing and treatment schedules confounded the ability to perform a meta-analysis. There was also great variability in the reporting of the maintenance or cumulative doses delivered and a variety of units were used to report dosing. The studies’ comparator groups were placebo (73% of the studies), another sublingual intervention without a placebo group (14%), or pharmacotherapy without placebo (13%). Primary outcomes of the studies included symptom scores, medication scores, quality of life, and safety. There was no uniform or consistent reporting of safety. Using the Grading of Recommendations Assessment, Development, and Evaluation Working Group guidelines, the evidence for each primary outcome was graded as high, moderate, low, or insufficient. The risk of bias was assessed as per the Cochrane Guidelines. Forty-six studies (73%) received industry support and were considered to have moderate or high bias.

RESULTS. Overall, the authors found moderate evidence across outcomes to support the use of SLIT for allergic rhinoconjunctivitis or asthma. For asthma, the strength of evidence in support of SLIT improving symptoms was graded as high. For allergic rhinoconjunctivitis, the evidence was graded as moderate strength. Evidence was similar in strength to support the use of SLIT in children (<18 years of age). Forty-seven (75%) of the trials mentioned safety. Because of the lack of a standard grading system, the authors concluded the evidence was insufficient to grade safety. Local reactions were more frequent in patients receiving SLIT (range, 0.2%–97.0%) than in the comparator groups (range, 3.0%–38.5%). Systemic reactions were rarely reported, but were more

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