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 mediation 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 extreme 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
common in the groups receiving SLIT than in comparator groups. There were no reported episodes of anaphylaxis, life-threatening reactions, or death in any treated subjects.

CONCLUSIONS. According to published trials, there is moderate strength of evidence supporting the effectiveness of SLIT for allergic rhinoconjunctivitis and asthma. There were significant limitations in the reporting of safety data, but no life-threatening adverse events were noted in the published trials.

REVIEWER COMMENTS. As per the accompanying editorial, several unanswered issues remain regarding the use of SLIT. Insufficient data were available to identify optimal dosing strategies. The optimal duration of therapy remains unclear, and the relative benefits of single versus multiple allergen therapy are unclear. These issues must be addressed before the Food and Drug Administration is likely to approve SLIT in the United States.

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PRIMARY IMMUNODEFICIENCY

Selective IgA Deficiency: Clinical and Laboratory Features in 118 Children in Turkey

PURPOSE. To investigate the clinical and laboratory features of children with selective immunoglobulin (Ig)A deficiency followed in a tertiary children’s hospital.

STUDY POPULATION. The medical records of 118 children (63 boys, 55 girls), median age 7 years (range 4–18 years), seen over a 5-year period were retrospectively reviewed.

METHODS. Patients with IgA levels <7 g/L and normal or elevated IgG and IgM were included in this study. Medical records were reviewed and laboratory studies included quantitative immunoglobulins, IgG subclasses, IgE, and autoantibodies. Medical history was evaluated for evidence of infections, allergic disease, and autoimmunity.

RESULTS. Sixty-one percent of these patients had been followed for >6 months, with 99 (84%) of the 118 patients with a history of recurrent infections, primarily upper respiratory infections. In addition, 51 (43%) of 118 had a history of allergic disorders, including predominantly rhinitis, asthma, and atopic dermatitis. Finally, 20 (17%) of 118 had a history of autoimmune disease with a wide range of disorders, including celiac disease and type 1 diabetes being the most prevalent.

CONCLUSIONS. Children with selective IgA deficiency may be more prone to upper respiratory infections, allergic disease, and autoimmunity.

REVIEWER COMMENTS. This report focuses on children with selective IgA deficiency referred to a tertiary children’s hospital, so it suffers from a potential for significant referral bias. However, in light of another recent publication on selective IgA deficiency (Jorgensen GH, et al. Clinical symptoms in adults with selective IgA deficiency: a case-control study. J Clin Immunol 2013;33:742–747), there is a real potential that selective IgA deficiency is associated with a greater degree of clinically significant symptomatology than has previously been appreciated. Importantly, in some cases these include recurrent sinopulmonary infections with encapsulated bacteria, whereas in others it is less clear while the incidence of allergic disease and autoimmunity is significantly higher. These observations appear to suggest that secretory IgA alone plays a less significant role in protecting the mucosal surfaces from bacterial infection while it may have a more prominent role in protecting the immune system at the level of the mucosa from interactions that increase the incidence of allergic disease and autoimmunity. There are no registries for selective IgA deficiency and the bulk of published studies from the past contend that the overwhelming majority of affected individuals are asymptomatic. Because of selection bias and/or small sample size in most reports to date, resolving the actual impact of selective IgA deficiency awaits studies in which ascertainment bias is dealt with and appropriate case controls are included together with long-term follow-up.


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Immunoglobulin Deficiencies: The B-Lymphocyte Side of DiGeorge Syndrome

PURPOSE OF THE STUDY. To better characterize humoral immunity in patients with DiGeorge syndrome.

STUDY POPULATION. An international cohort of 1023 patients with DiGeorge syndrome was used in this investigation. This included data from 21 countries and 40 different contributors, including 662 records from the US Immunodeficiency Network, 381 from the European Society for Immunodeficiencies, 327 from the Children’s Hospital of Philadelphia, and fewer than 50 patients per institution from the remaining contributors.

METHODS. The investigators defined a low serum immunoglobulin G (IgG) value as <500 mg/dL and a low CD3+ count as <500 cells/mm³ to stratify patients for the
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