GC by inhaler alone or inhaler in combination with other routes. Nearly two-thirds of the children had asthma, and another 15% had asthma plus another condition being treated with GC. Almost one-third of the children were treated with ICS alone. The most commonly used ICS was fluticasone, with most children receiving doses of ~500 μg/day.

CONCLUSIONS. The estimated incidence of symptomatic AS in the pediatric population is small, but it is potentially much higher in at-risk groups (children treated with GC). The close monitoring of growth and asking about nonspecific symptoms such as fatigue, nausea, and myalgia may help with earlier detection. To reduce the risk of AS, physicians must be aware that AS can occur, evaluate GC doses frequently, and use the lowest effective dose.

REVIEWER COMMENTS. This study is a good reminder that we must be aware of the risk of adrenal suppression in children treated with glucocorticoids. Although inhaled corticosteroids have dramatically improved asthma care, the close monitoring of growth and attention to nonspecific or vague symptoms suggesting AS is essential. Our goal for asthma treatment is to use the least amount possible to keep asthma in control.

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Tiotropium Add-on Therapy in Adolescents With Moderate Asthma: A 1-Year Randomized Controlled Trial

Hamelmann E, Bateman ED, Vogelberg C, et al. *J Allergy Clin Immunol*. 2016;138(2):441–450.e8

PURPOSE OF THE STUDY. Phase II studies in children and adolescents have demonstrated that tiotropium is an effective add-on to inhaled corticosteroid (ICS) maintenance therapy. This study sought to assess the safety and efficacy of once-daily tiotropium Respimat added to ICS in a phase III trial in adolescents with moderate symptomatic asthma.

STUDY POPULATION. Eligible patients were aged 12–17 years with histories of asthma of >3 months and who were symptomatic at screening, as defined by the 7-question Asthma Control Questionnaire (ACQ-7). Patients were required to have been receiving ICS +/− long-acting β agonist (LABA) or leukotriene receptor antagonist (LTRA), FEV1 60% to 90% of predicted normal, at least 12% reversibility after albuterol, FEV1 variability within 30% between screening and randomization, and no history of smoking or other lung disease.

METHODS. In this 48-week, double-blind, placebo-controlled, parallel-group study, 398 patients were randomized to receive 5 mcg or 2.5 mcg of tiotropium or placebo via a Respimat device once daily as an add-on to usual ICS, with or without LTRA. LABA use was not permitted. The primary efficacy end point was change from baseline in FEV1 within 3 hours after dosing at week 24. Blinded efficacy and safety monitoring continued to week 48. Secondary end points included trough FEV1, area under the curve (AUC) for FEV1 within 3 hours after dosing, various other pulmonary function measures after 24 weeks of treatment, time to first asthma exacerbation, asthma control (ACQ-6 and ACQ-7), and quality of life as evidenced with the Asthma Quality of Life Questionnaire with Standard Activities (ACLQ).

RESULTS. Both active treatment doses resulted in significantly greater improvement in the FEV1 primary end point versus the placebo ($P < .001$ for 5 mcg, $P < .01$ for 2.5 mcg). Trough FEV1 improved significantly only for the 5-mcg dose versus the placebo ($P < .03$). Also significant were changes in FEV1 AUC for both 5-mcg ($P < .001$) and 2.5-mcg ($P < .008$) doses. Trends for improvement in asthma control and health-related quality of life were observed over the 48-week course but were not statistically significant. No significant side effects occurred with use of either active dose.

CONCLUSIONS. Once-daily tiotropium significantly improved lung function and was safe and well tolerated as an add-on to maintenance ICS in adolescents with moderate symptomatic asthma, especially at the 5 mcg dose. This finding adds to the growing body of evidence supporting the inclusion of tiotropium as an option in step therapy for uncontrolled asthma in adolescents.

REVIEWER COMMENTS. The authors point out that there is considerable heterogeneity in individuals' responses to LABAs and long-acting anticholinergics, and there are no clinical markers we can employ to choose 1 agent versus the other. So, we are not in the "either or" circumstance, at least not yet, in the adolescent population. Given current evidence, tiotropium could be considered as a treatment option for adolescents with moderate persistent disease, in combination with ICS +/− LTRA.

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Real-life Effectiveness of Omalizumab in Severe Allergic Asthma Above the Recommended Dosing Range Criteria

Hew M, Gillman A, Sutherland M, et al. *Clin Exp Allergy*. 2016;46(11):1407–1415

PURPOSE OF THE STUDY. To determine if omalizumab (anti-IgE) above the standard dosing ranges can be beneficial in severe asthmatics and compare responses to patients who are within normal dosing ranges.

STUDY POPULATION. In Australia, most patients receiving government-funded omalizumab are enrolled in the Australian Xolair Registry. This registry includes 21 sites, with patients ≥12 years old who have severe, uncontrolled asthma; patients with serum IgE levels ≥76 IU/mL; and patients who have failed to achieve adequate control with optimized asthma therapy.

METHODS. Registry data were obtained (including demographics, medical history, disease status and control, current treatment, lung function, medical resource use, and patient-reported outcomes) by using the Asthma Control Questionnaire (ACQ-5) and the Asthma Quality of Life Questionnaire (AQLQ). Patients were assessed at 6, 12, 18, and 24 months after starting omalizumab. Participants were classified according to their baseline weight and/or IgE level and whether these variables were above or within the standard dosing table (Australia and the US use the same dosing tables). The primary outcome measured was the change in symptom control as measured by the ACQ-5. Secondary outcomes measured were changes in the AQLQ mean score and pre- and postbronchodilator forced expiratory volume in 1 second (FEV1). In a small portion of patients, changes in hospital admissions and exacerbations were also evaluated.

RESULTS. A total of 179 participants were included, with 55 (31%) dosing above the standard dosing and 124 (69%) within standard dosing. Above-range participants had higher baseline IgE levels (812 IU/mL; range 632–1747) compared with in-range participants (209 IU/mL; range 134–306). Baseline AQLQ scores were significantly lower for above-range asthmatics versus in-range patients (3.21 [SD 1.14] vs 4.01 [SD 1.21, $P = .02$]). Above-range participants received a median dose of omalizumab of 750 mg (IQR 650–750) compared with in-range participants who received a median dose of 450 mg (IQR 300–600). After 6 months of therapy, there was a statistically significant improvement in ACQ-5 scores for both the above-range group (3.61 to 2.10, $P < .0001$) and the in-range group (3.47 to 1.93, $P < .0001$). AQLQ also reflected statistical improvement for both groups (above-range group: 3.22 to 4.41; in-range group: 3.71 to 4.88, $P < .0001$). Above-range participants demonstrated statistically significant improvements in pre- and postbronchodilator FEV1 that were similar to the changes seen for the in-range participants. There was no difference in the exacerbation rate for either group.

CONCLUSIONS. Omalizumab dosing (750 mg monthly) in severe asthmatic patients who are above established criteria because of weight or baseline IgE levels demonstrate significantly improved symptom control, quality of life measures, and lung function, and these improvements are similar to changes seen in individuals treated with in-range doses.

REVIEWER COMMENTS. These results provide literature support for above-range dosing of omalizumab (Xolair) for severe asthmatic patients. According to EPR-3 for asthma management, severe allergic asthmatic patients who are poorly controlled on combination therapy are good candidates for targeted therapy with this monoclonal antibody. Dose and frequency of omalizumab in the US are based on weight and total IgE level, leading to a higher calculated dose for patients with either a higher starting IgE level or elevated body weight. Patients with severe persistent asthma who are highly atopic experience significant costs and morbidity, with decreased options for asthma treatment if their IgE level is too high. Additional studies of omalizumab dosing for this group of patients are needed to further support its benefit.

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Efficacy and Safety of Benralizumab for Patients With Severe Asthma Uncontrolled With High-Dosage Inhaled Corticosteroids and Long-acting β2-agonists (SIROCCO): A Randomised, Multicentre, Placebo-Controlled Phase 3 Trial

Bleecker ER, FitzGerald JM, Chanez P, et al. *Lancet*. 2016;388(10056):2115–2127

PURPOSE OF THE STUDY. To assess the safety and efficacy of benralizumab, a monoclonal antibody against the interleukin-5 (IL-5) receptor α that depletes eosinophils for patients with severe, uncontrolled asthma with eosinophilia.

STUDY POPULATION. Between 2013–2015, 2681 patients were enrolled in this randomized, double-blind, parallel-group, placebo-controlled phase 3 study in 17 countries. Inclusion criteria were being 12–75 years old, having a physician-based diagnosis of asthma for at least 1 year, and having at least 2 exacerbations while on high-dose inhaled corticosteroids and long-acting β2-agonists in the previous year.

METHODS. Patients were randomly assigned (1:1:1) to subcutaneous benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W) or a placebo Q4W for 48 weeks as add-on therapy. Patients were stratified 2:1 based on blood eosinophil counts of greater or less than 300 cells per μL. The primary end point was the annual exacerbation rate ratio.

RESULTS. Compared with the placebo, Q4W and Q8W benralizumab reduced the annual asthma exacerbation rate by up to 51% over 48 weeks and significantly improved prebronchodilator FEV1 at week 48. Compared with the placebo, Q8W benralizumab significantly improved asthma symptoms. The most common adverse events were worsening asthma and nasopharyngitis.

CONCLUSIONS. These results confirm the efficacy and safety of benralizumab for patients with severe asthma and elevated

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