

What Do “Real Life” Studies Tell Us About Asthma Controllers?

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National and international guidelines for asthma therapy stress the importance of asthma control.¹ Achieving control means focusing on both impairment and risk. Risk is evaluated by the level of pulmonary function and history of recent exacerbations, both of which are related to the risk of future asthma morbidity. Asthma exacerbations are one of the most common reasons for emergency department (ED) visits in the United States. Establishing control, then, is not just about control of symptoms and use of medications but also about the prevention of exacerbations. The clinician is faced with several choices in managing a child with poorly controlled asthma and frequent exacerbations. Multiple randomized, controlled clinical trials have favored the use of inhaled corticosteroids (ICS) over leukotriene receptor antagonists (LTRA) in the reduction of exacerbations.²⁻⁶ There have been other controlled trials, however, that have shown equivalence in exacerbation prevention with LTRA.^{5,7} All of these trials have demonstrated the superiority of ICS for symptom control and medication use.⁴⁻⁷ Critics of randomized, controlled trials believe that patients in these trials are not representative of patients encountered in the usual clinical environment. As a result, “real life” or “pragmatic” trials have been undertaken in attempts to simulate what occurs in the everyday practice of medicine.

One such trial is the study published by Wu et al,⁸ in this issue of *The Journal of Allergy and Clinical Immunology: In Practice*, a large retrospective study in children, 4 to 17 years of age, with controller-naïve asthma, who had experienced at least 1 exacerbation that required an ED visit, hospitalization, or oral corticosteroids in the previous 12 months, and who were started on a LTRA, ICS, or ICS in combination with a long-acting β -agonist. They then examined the numbers of days to the same types of exacerbations in the cohort after the start of the new controller medications.⁸ This study evaluated 26,191 children from 6 private health plans and the Tennessee Medicaid program. The choice of controller medication was left to the patient's physician. The patients in the private health plan and the Medicaid patients were analyzed separately because of differences in race, type of controller medication dispensed, and rates of exacerbations.⁸ The investigators also performed separate analyses, depending on the presence or absence of allergic rhinitis.⁸ Statistical methods were

applied to control for differences in adherence and baseline confounding by indication. An important point was that the age group selected was less likely to experience spontaneous resolution of disease. Findings of the study were that, within the Medicaid population, there were higher exacerbation rates in the patients treated with ICS and in the patients in the health plan, there were no differences in the ED visits among the groups, but more oral corticosteroids courses were prescribed for the ICS group compared with the LTRA group or ICS–long-acting β -agonist group. There were some indications in both populations that the subjects who started on ICS may have been sicker. There also was a differential in adherence. Adherence was poor overall but worse in the ICS and ICS–long-acting β -agonist groups.

Recent studies that used the same approach have shown mixed results.⁹⁻¹¹ A recent study of adults and adolescents, which overlaps the age group in the study by Wu et al,⁸ showed little difference in asthma quality of life scores, rate of asthma control, or exacerbations between ICS and LTRA⁹ over a 2-year period, but equivalence in quality of life, the primary outcome measurement, although demonstrated early in the trial, was not evident at 2 years. In addition, more subjects in the LTRA-treated group needed to cross over to additional medications during the follow-up period. This group also experienced issues with adherence, which was lower for the ICS group. Another retrospective study that involved similar numbers of children of the same age group,¹⁰ also found that exacerbations were higher in the ICS group compared with the LTRA group but only for those who had not had a prior exacerbation. Adherence with this group also was poor but was greater for the LTRA group. However, a retrospective study that used pharmacy and medical encounter databases, although written by industry employees, was able to show better prevention of exacerbations with ICS.¹¹ This study also used statistical methods to control for confounding. Interesting aspect of the study by Wu et al⁸ are the results of patients with allergic rhinitis, who did better when on LTRA than on ICS. This has been demonstrated in another study¹² and possibly suggests that effectiveness of the LTRA in treating allergic rhinitis increases the adherence with this medication.

The weaknesses in the study by Wu et al,⁸ in common with other “real life” studies, are the retrospective nature, the difficulty with adherence, lack of control of the original assignment of controller medication, lack of a control group, and the heterogeneity of the subjects.^{9,13} These characteristics tend to reduce the observable differences between treatments. Retrospective studies do not allow for delineation of asthma phenotypes or the true severity of asthma. Selection of large populations based on a discharge diagnosis of asthma is likely to include a widely heterogeneous population, some of whom may not actually have asthma. Enrolling patients with previous ED visits, hospitalizations, or a course of oral corticosteroids increases the chances that such patients do indeed have asthma but not all would

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necessarily be candidates for controller medications. Such a population would likely consist of a large proportion of children with intermittent or mild persistent disease severity who would be expected to do equally well with LTRA or ICS therapy and could do as well with no therapy at all. Active control equivalence trials, which include “real life” trials and noninferiority trials, do not, by themselves, demonstrate efficacy. Equivalence may occur when both medications are effective but also when both are ineffective.¹³ Poor adherence, particularly adherence differential, can create a bias toward the finding of equivalence.¹⁴

Do studies such as the study by Wu et al⁸ and other active control equivalence studies help the practitioner in determining which controller medication to use when confronted with the child with poorly controlled asthma? Is the application of these results without consideration of the asthma phenotype likely to miss the mark in the era of individualized therapy for asthma? Randomized, controlled trials do focus on well-defined, tightly controlled populations of children with asthma, and these results are certainly not generalizable to all children with asthma. But studies that involve populations of children with asthma in the “real world” are not necessarily generalizable to the individual patient in the office.

Patients with asthma who are seen in all practices, whether specialist or generalist, have a variety of phenotypes, each with different symptom patterns, triggers, and responses to medications. The key to individualized management of asthma is familiarity with treatments that have been shown to be effective for certain types of patients, as demonstrated in published randomized trials. Determining therapy based on pragmatic trials could place all patients with asthma into the same bucket, with the impression that choosing the medication with the best adherence might be the best approach, regardless of the asthma phenotype.

Can active control equivalence trials do harm? There may be a real risk that insurance company formulary committees may use such studies to limit choices for asthma therapy. What the clinician really needs is more prospective comparative efficacy research in well-characterized populations to identify the best approach to therapy for the individual child with asthma and ways to best promote adherence to the selected therapy.

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