Original Article

Use of Leukotriene Receptor Antagonists Are Associated with a Similar Risk of Asthma Exacerbations as Inhaled Corticosteroids

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What is already known about this topic? Results of randomized clinical trials found that inhaled corticosteroids have greater efficacy than leukotriene receptor antagonists to prevent exacerbations of childhood asthma under controlled circumstances. Few studies compared the effectiveness of these controller medication regimens under real-life conditions.

What does this article add to our knowledge? This study found that the risk of emergency department visits, hospitalizations, and oral corticosteroids did not differ between children who initiated leukotriene antagonist and those who initiated inhaled corticosteroid in 5 health plans and a state Medicaid population. These findings may be explainable by leukotriene antagonist having similar effectiveness as inhaled corticosteroid in real-life usage.

How does this study impact current management guidelines? Analysis of the results of this study suggests that current national asthma management guidelines are not being followed.

BACKGROUND: Based on results of clinical trials, inhaled corticosteroids (ICS) are the most-effective controller medications for preventing asthma-related exacerbations, yet few studies in real-life populations have evaluated the comparative effectiveness of ICS.

OBJECTIVE: To determine the likelihood of asthma exacerbations among children with asthma after initiation of controller medications: ICS, leukotriene antagonists (LTRA), and ICS−long-acting β-agonist (LABA) combination therapy.

METHODS: This was a retrospective cohort study of subjects who were part of the Population-Based Effectiveness in Asthma and Lung Diseases Network. We conducted Cox regression analyses by adjusting for baseline covariates, adherence by using proportion of days covered, and high-dimensional propensity scores. The main outcome measurements were emergency department visits, hospitalizations, or oral corticosteroid use.

RESULTS: Our population included 15,567 health plan subjects and 10,624 TennCare Medicaid subjects with uncontrolled asthma. Overall adherence to controller medications was low, with no more than 50% of the subjects refilling the medication after the initial fill. For subjects with allergic rhinitis, the subjects in TennCare Medicaid treated with LTRAs were less likely to experience ED visits (hazard ratio 0.44 [95% CI, 0.21-0.93]) compared with the subjects treated with ICS. For all other groups,

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Abbreviations used
ED- Emergency department
hdPS- High-dimensional propensity score
HPHC- Harvard Pilgrim Health Care
HR- Hazard ratio
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-agonist
KPGA- Kaiser Permanente Georgia
KPNC- Kaiser Permanente Northern California
KPNW- Kaiser Permanente Northwest
LTRA- Leukotriene antagonist
PDC- Proportion of days covered
PEAL- Population-based Effectiveness in Asthma and Lung Diseases
TennCare- Tennessee Medicaid

the subjects treated with LTRA or ICS-LABA were just as likely to experience ED visits or hospitalizations, or need oral corticosteroids as the subjects treated with ICS. CONCLUSION: Risks of asthma-related exacerbations did not differ between children who initiated LTRA and ICS. These findings may be explainable by LTRA, which has similar effectiveness as ICS in real-life usage by residual confounding by indication or other unmeasured factors. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:607-13)**

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In numerous pediatric clinical trials that compare therapy of inhaled corticosteroids (ICS) to leukotriene antagonists (LTRA), ICS have been found to have superior efficacy.[1-4] ICS have been found to improve lung function, decrease the number of asthma-related hospitalizations, reduce emergency department (ED) visits, and limit the use of oral corticosteroids.[1-4] Thus, evidence-based guidelines generated by expert consensus suggest that ICS should be the preferred first-line therapy for patients with persistent asthma, with LTRAs as an alternate treatment.[5] Results of some clinical trials that compared combination ICS and long-acting β_2-agonists (LABA) versus high-dose ICS in children suggested that ICS-LABAs are superior to ICS in improving symptoms, increasing lung function, and decreasing exacerbations that require oral steroids; however, results of other clinical trials indicate that ICS monotherapy may be more effective than LTRA or ICS-LABA in reducing the risk of exacerbations, and ICS may be as effective as ICS-LABA in reducing the time to the first exacerbation.[6-8]

Findings from clinical trials may not translate into improved health outcomes in clinical practice because patient selection factors, such as asthma severity, comorbidities, and adherence, may differ in real-world practice compared with clinical trials.[9] A lack of information on the relative effectiveness of these regimens in real-world settings could lead to variability in practice.[1-3,10-14] To our knowledge, to date, no studies have compared the real-world effectiveness of all 3 major controller regimens with children in preventing asthma-related exacerbations. Anecdotal evidence indicates that, in clinical practice, many providers commonly choose LTRAs or ICS-LABAs rather than ICS as first-line controller therapy. Parental concern about the potential effects of ICS on linear growth could prompt clinicians to start patients on LTRAs rather than ICS.[15,16] Medication adherence could influence the effectiveness of regimens in practice because adherence to medications in clinical trials is often higher than in real-life practice. There is evidence that adherence to LTRAs is higher than to ICS in real-life settings.[17] The objective of this study was to evaluate health care utilization events among children with probable persistent asthma after initiation of each of the major controller medication regimens: ICS, LTRAs, and ICS-LABAs.

METHODS

Study design

This was a retrospective cohort study of children with asthma in the Population-based Effectiveness in Asthma and Lung Diseases (PEAL) Network. The network includes data from 6 health plans: Harvard Pilgrim Health Care; HealthPartners; Kaiser Permanente Northern California; Kaiser Permanente Georgia; Kaiser Permanente Northwest; and TennCare Medicaid, the Tennessee Medicaid plan. The institutional review board at each site approved this study. Electronic data from the subjects from each of the 6 sites were pooled to form the PEAL Data Warehouse, which includes information on subject demographics, enrollment type, dispensing medications, health care resource utilization, and smoking status.

PEAL asthma population

Subjects were potentially eligible for the PEAL asthma population if they had any discharge diagnosis for asthma based on the International Classification of Diseases, Ninth Revision code for asthma (493.xx) during an acute inpatient hospital stay, ED visit, ambulatory visit, or nonacute institutional stay during the period of January 1, 2004, to December 31, 2010. This time window varied for each site by up to 1 year, based on data availability. Subjects were excluded if they had a diagnosis of cystic fibrosis, immunodeficiency, bronchiectasis, hereditary and degenerative diseases of the central nervous system, psychoses, mental retardation, congestive heart failure, pulmonary hypertension, or pulmonary embolism based on International Classification of Diseases, Ninth Revision codes. We identified 218,019 subjects in the PEAL Network who had uncontrolled asthma in the baseline period, which meant that they had at least 1 eligible health care encounter (hospitalization, ED visit, or dispensing of oral corticosteroids of 3 days or more) and continuous enrollment during the 12-month period before dispensing an ICS, LTRA, or ICS-LABA. The definition of uncontrolled asthma occurred before dispensing an ICS, LTRA, or ICS-LABA. Patients who were dispensed individual ICS and LABA inhalers on the same day or combination ICS-LABA inhalers were included in the ICS-LABA group. If the patients had multiple eligible episodes of medication dispensing, we included the first episode. We removed 13,830 subjects who did not initiate monotherapy (or ICS-LABA) of one of the controller medications of interest, and 204,189 subjects remained. Of the 204,189 subjects, 84,044 subjects were incident users (no prior controller medication use during the 12-month baseline period). The 26,191 pediatric subjects ages 4-17 years who were incident users were the focus of this analysis.

Statistical analyses

We conducted bivariate analyses to evaluate associations between the predictor variables and outcomes, by controller