Demographic Predictors of Leukotriene Antagonist Monotherapy Among Children with Persistent Asthma

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Objective To describe the children with persistent asthma receiving non-preferred controller therapy in the form of leukotriene receptor antagonist monotherapy (LTRAM).

Study design In this cross-sectional study, we analyzed 2007-2009 South Carolina Medicaid data of children aged 2- to 18 years with persistent asthma, defined by Healthcare Effectiveness Data and Information Set (HEDIS). Those without either LTRAM or inhaled corticosteroids (ICS) were excluded. With multivariable logistic regression modeling, we compared the outcome of LTRAM with the primary predictor of age and adjusted for covariates of race, sex, HEDIS class, rurality, and disease severity. We also used negative binomial regression to compare outcomes of albuterol and oral steroid claims, outpatient and emergency department visits, and hospitalizations with predictors of LTRAM vs ICS therapy.

Results A total of 19 512 patients with asthma aged 2- to 18-years were studied: 2658 (13.6%) without controllers were excluded, 2508 (12.9%) received LTRAM, and 14 346 (73.5%) received ICS. Age, race, rurality, and HEDIS classification were all significantly associated with LTRAM (all $P < .01$): 5- to 13-year-olds relative to children <5 years old (OR 1.46, 95% CI 1.30-1.64), Caucasians relative to African Americans (OR 1.40, 95% CI 1.27-1.53), and rural children relative to urban (OR 1.18, 95% CI 1.08-1.3) were all more likely to receive LTRAM. Albuterol, oral steroid, and outpatient visits were lower in LTRAM ($P < .01$). No difference was detected in emergency department visits or admissions.

Conclusions Children 5- to 13-years of age, rural children, and Caucasian children were more likely to receive LTRAM. Uncovering provider rationale and practices as well as patient influences on this prescribing pattern may be helpful in optimizing asthma controller therapy. *(J Pediatr 2014;164:827-31)*.

In the US, asthma is the most common chronic disease of childhood, responsible for significant morbidity and healthcare utilization.[1,2] The last 2 decades have witnessed an increase in the use of preventative asthma medication among children and adolescents; however, controller use continues to be poor among those with persistent asthma.[1-3] The importance of asthma control cannot be understated as poor control leads to increased healthcare utilization and decreased quality of life.[4] In 2007, the National Asthma Education and Prevention Program updated management guidelines for the treatment of persistent asthma, again promoting inhaled corticosteroids (ICS) as the preferred therapy to manage persistent asthma.[5] Concurrently, leukotriene receptor antagonists (LTRA) have also emerged as a non-preferred, adjunctive therapy for the treatment for persistent asthma in clinical practice.[3,5,6]

LTRA agents control inflammation by a pathway distinct from ICS agents. Purported advantages of LTRA agents include chewable oral formulation and once daily administration.[7-9] Despite their advantages, a 2012 Cochrane Systematic review and other previous studies have not only demonstrated LTRA to be less clinically effective than ICS in the management of persistent asthma but also less cost-effective.[10-12] In 2005, the Montelukast Study of Asthma in Children study, a multicenter, randomized, double-blind, noninferiority trial, evaluated 6- to 14-year-olds with asthma and found that montelukast was not only inferior to fluticasone in the number of rescue-free days, but fluticasone was significantly superior in nearly all other outcome measures including forced expiratory volume in 1 second measures, total days of beta-receptor agonist use, and quality of life.[13] In 2011, a United Kingdom pragmatic study evaluating LTRA monotherapy (LTRAM) and ICS demonstrated that there was no difference in reported quality of life at 2 months; however, by 2 years, LTRAM was found to be significantly inferior.[14]

Despite the superior performance of ICS in clinical trials, the management of persistent asthma is very heterogeneous. Asthma controller therapy remains underprescribed, especially in younger children, and LTRA continue to be prescribed even as monotherapy.[15-18] Several factors may account for this potential

ED	Emergency department
HEDIS	Healthcare Effectiveness Data and Information Set
ICD-9	*International Classification of Diseases, 9th revision*
ICS	Inhaled corticosteroid
LTRA	Leukotriene receptor antagonist
LTRAM	Leukotriene receptor antagonist monotherapy

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association, including concern regarding the potential adverse effects of steroids on growth,[19] disruptions of the hypothalamic-pituitary-adrenal axis,[19,20] and the medication delivery advantages of LTRA. The management of persistent asthma is further complicated by differences among varying ethnic and racial populations. Specifically, persistent asthma carries significantly higher morbidity among African American children.[1,3,21] Disparities also exist between urban vs rural children with asthma. Urban children are likely to experience greater asthma burden,[21] and their rural counterparts are less likely to receive ICS following an acute exacerbation requiring emergency department (ED) services.[16]

In this study, we sought to describe children with persistent asthma who receive non-preferred controller medications in the form of LTRAM. Our hypothesis is that younger children with persistent asthma are more likely to receive LTRAM possibly because of greater adherence secondary to ease of administration and sidestepping the potential adverse effects of ICS.

Methods

We conducted a cross-sectional analysis utilizing 2007-2009 South Carolina Medicaid data. Patients aged 2- to 18 years with at least 1 calendar year of continuous Medicaid enrollment were included. We isolated all encounters with a primary diagnosis of asthma using *International Classification of Diseases, 9th revision* (ICD-9) codes 493.00-493.02, 493.10-493.493.12, 493.20-493.22, 493.8, and 493.9. From this group, we eliminated all patients with the following comorbid conditions using ICD-9 codes: exercise-induced asthma, cystic fibrosis, bronchiolitis, respiratory syncytial virus, intellectual disability (moderate, severe, or profound), congenital heart disease, sickle cell disease, chronic respiratory disease arising in the perinatal period, tracheostomy, gastrostomy, or any other artificial opening of the gastrointestinal tract.[22] We also excluded individuals who were not on controller therapy, either ICS or LTRA, because the focus of our investigation was to study patients using non-preferred compared with preferred preventative therapy for persistent asthma.

Only children with persistent asthma were included in our analysis because this population would potentially have the greatest potential of optimized management. We defined persistent asthma by the Healthcare Effectiveness Data and Information Set (HEDIS) criteria as individuals who had, in any 12 months, any of the following: (1) any hospitalization for asthma; (2) any ED visit for asthma; (3) 4 or more outpatient asthma visits and 2 or more asthma medication dispensing events; or (4) 4 or more asthma medication (eg, short-acting beta agonist, ICS, leukotriene modifier) dispensing events. HEDIS has been validated to be consistent with survey-defined persistent asthma and has been used in previous literature.[23,24] After being defined as having persistent asthma, an individual maintained persistent asthma status for the remainder of this study. This study was approved by the Medical University of South Carolina institutional review board prior to initiation of this study.

The primary outcome of LTRAM was described in bivariate analyses with demographic variables (age, sex, and race), HEDIS classification, and county of residence (rural or urban) as a proxy for access to care. As LTRAM was the primary interest in the present study, children with claims for both LTRA and ICS were grouped as being controlled with ICS. Ages were stratified to 2-4, 5-13, and 14-18 years old. Though there has not been any standardization in age group in asthma studies, we chose to stratify ages in this manner to illustrate patterns across school age groups. Patient's race was self-identified and classified as African American, Caucasian, Hispanic (Hispanic ethnicity is treated as a separate category, equal to race, in the South Carolina Medicaid data), or other for the purposes of this study. We used the Metropolitan Statistical Area definition of urban for the analysis, and counties not qualified as urban were labeled rural.[16,25,26] To control for potential confounding, in which a child with asthma was designated to be persistent, the manner in which an individual qualified by HEDIS criteria (above) was also included in multivariable modeling. To account for disease severity, study subjects were dichotomized to have severe asthma if a child required more than 6 albuterol refills per year.[16] Prespecified secondary analyses comparing LTRAM vs ICS therapy in terms of disease burden and healthcare utilization were undertaken with outcome variables of albuterol and oral steroid claims, as well as total number of outpatient visits, ED visits, and hospital admissions.

Statistical Analyses

We used χ^2 tests to compare demographic characteristics of patients who receive LTRAM and those who received ICS. We calculated the adjusted relationship among all variables for the primary outcome variable of LTRAM vs ICS by multivariable logistic regression. To account for overdispersion of count variables (ie, the amount of variance of medication claims and healthcare utilization in the study cohort was greater than expected), unadjusted negative binomial regression modeling was used to evaluate secondary analyses comparing LTRAM vs ICS with outcome variables of albuterol and steroid claim rates, as well as outpatient visits, ED visits, and hospitalization. All statistical analyses were performed with SAS statistical software, v. 9.3 (SAS Institute, Cary, North Carolina).

Results

There were 16 849 children with persistent asthma in the final analysis (**Figure**; available at www.jpeds.com). **Table I** demonstrates the distribution of study covariates. The study population was majority male, African American, and lived in urban areas. The mean age of study participants was 8.9 years (SD 4.4 years); 2508 children with asthma had claims for only LTRA, 5031 had claims for only ICS, and 9310 had claims for both LTRA and ICS