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

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Abstract

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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, 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;■: ■-■)

Keywords

Asthma; Controller medications; Effectiveness; Inhaled corticosteroids; Leukotriene antagonist; Long-acting β -agonist

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 medication regimen (ICS, LTRA, and ICS-LABA). We evaluated the following predictor variables that might confound the relationship between controller medication regimens and outcomes: age; sex; race; asthma-related ED visits, hospitalizations, and outpatient visits in the 365 days before the initial fill of controller medication; and dispensing oral corticosteroids or short-acting β -agonists in the 365 days before initial fill of the controller medication. In addition, we evaluated the following predictor variables: the modified Charlson score, which included all diseases that comprise the Charlson Comorbidity Index, except chronic pulmonary disease because it includes the diagnosis of asthma; the number of medications in the prior 365 days (counted by generic names) because it has been demonstrated to account for severity of illness¹⁸; and a history of additional comorbid illnesses, which included allergic rhinitis, gastroesophageal reflux disease, and acute respiratory infection.¹⁹ Our time-to-event outcomes were the number of days since the initial dispensing to the first occurrence of any asthma-related ED visit, hospitalization, or fill of oral corticosteroids in the 365 days after the initial dispensing of the controller medication. The subjects were censored at disenrollment if disenrollment occurred before 365 days, 30 days after they switched to or augmented a controller medication from a different class, or 365 days after the first dispensing of the initiated controller medication, whichever occurred first.

We used the Cox proportional hazards regression as the base model to analyze the time-to-event outcomes and to account for adherence as a time-varying covariate, which is defined by using the proportion of days covered (PDC) based on a moving 30-day window.²⁰ Because all the subjects started off with a 30-day dispensing of medication, they were guaranteed a minimum of 30 days of good adherence; thus, all of the analyses ignored the first 30 days after initial dispensing. Specifically, at each time t , the PDC was defined as the proportion of days with medication coverage during the previous 30 days. To estimate the length of time on each medication, we used the number of days supply for the medication dispensing. We calculated the PDC for the initiated controller medication and then created a dichotomized indicator for adherence based on a PDC of ≥ 0.75 because a prior study demonstrated that adherence as measured by PDC of >0.75 was associated with decreased numbers of asthma exacerbations.²¹

We used 2 confounding adjustment methods, the covariate-adjusted regression and the high-dimensional propensity score (hdPS) regression, in conjunction with the base Cox regression model, to examine the associations between the initiated controller medication and the outcomes. The covariate-adjusted regression analysis adjusts for confounding by including the predefined covariates (Table I) directly in the regression model. The hdPS analysis was conducted to further reduce residual unmeasured confounding. In the hdPS analysis, we first ascertained a list of empirical covariates by using a semi-automatic algorithm from electronic health care data.^{22–24} We used 7 data dimensions in the electronic health care data, including inpatient diagnosis, inpatient procedure, outpatient diagnosis, outpatient procedure, ED diagnosis, ED procedure, and medication dispensing during the 365 days before the index date. We then fitted a logistic regression model to estimate the hdPS, which are defined as the conditional probability of receiving the exposure of interest given the predefined covariates and the derived empirical covariates. We conducted 2 separate propensity scores: one that compared ICS versus LTRA and a second that compared ICS versus ICS-LABA. We then adjusted for the hdPS instead of the predefined covariates in the extended Cox regression model. The Cox regression analyses were conducted among all 26,191 incident users.

We conducted separate analyses for the TennCare population and the pooled health plan population because the populations were quite different with respect to race, dispensing controller medications, and rates of asthma-related exacerbations. Among each subsample, we also conducted separate analyses for the subjects who had a diagnosis or did not have a diagnosis of allergic rhinitis in the prior 365 days due to the possibility that LTRAs could be used for both allergic rhinitis and persistent asthma.²⁵ In addition, symptoms from allergic rhinitis could trigger asthma-related exacerbations.²⁶ All analyses were conducted by using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Study population

Of the 26,191 subjects who met our inclusion and exclusion criteria, 41% (10,624) were from TennCare Medicaid and 59% (15,567) were from the health populations. In TennCare Medicaid, 38% initiated treatment with an ICS, 7% initiated treatment with an ICS-LABA, and 55% filled an LTRA; in the health plans, 87% filled an ICS, 5% filled an ICS-LABA, and 8% filled an LTRA. The demographic and baseline data are presented in Table I.

TennCare Medicaid population.—In TennCare Medicaid, 55% were white, 36% were black, 4% were Latino, 0.1% were Asian, and 4% were other or unknown. The subjects who filled ICS-LABAs were more likely to be girls (47%) compared with subjects who filled ICS and LTRAs, although this was not statistically significant (43% and 43%, respectively; overall $P = .082$). White subjects were more likely to fill LTRAs (60%) than ICS and ICS-LABAs (48% and 55%, respectively); however, black subjects filled ICS and ICS-LABA (41% and 39%, respectively) more frequently than LTRAs (31%).

In the year before initiating controller medications, the subjects who filled LTRAs were less likely to have an asthma-related ED visit (34%) compared with the subjects who filled ICS

and ICS-LABAs (41% and 42%, respectively; overall 0.001). The subjects who filled LTRAs and ICS-LABAs were less likely to have an asthma-related hospitalization than those who filled ICS (5% and 7% vs 13%, respectively; overall $P < .001$). The subjects who filled LTRAs also were less likely to have asthma-related outpatient visits (26%) compared with subjects who filled ICS (32%) and ICS-LABAs (34%, overall $P < .001$). The frequencies of outcomes in the year after controller medication dispensing are provided in Table II. In subjects who met criteria for continuous enrollment, 21% of patients in TennCare Medicaid who filled an ICS experienced an exacerbation compared with 17% of patients who filled an ICS-LABA or 14% who filled an LTRA ($P < .001$).

Health plan populations.—In the health plans, 30% of the subjects were white, 11% were black, and 15% were Latino. The subjects whose ICS-LABAs were filled were more likely to be girls (44%) compared with the subjects whose ICS and LTRAs (41% and 42%, respectively; overall $P = .11$) were filled. In the 1 year before dispensing controller medications, the subjects in the health plan populations whose LTRAs were filled were less likely to experience asthma-related ED visits (19%) compared with subjects whose ICS and ICS-LABAs were filled (24% and 24%, respectively; overall $P < .001$) and asthma-related outpatient visits (40%) compared with subjects whose ICS and ICS-LABA were filled (45% and 49%, respectively; overall $P < .001$). The subjects whose LTRA and ICS-LABA were filled were more likely to have had 2 or more dispensings of oral corticosteroids (20% for LTRA and ICS-LABA vs 14% for ICS; overall $P < .0001$). In the health plans, there was no difference in the frequency of ED visits because 6% of patients whose ICS, ICS-LABA were filled, and LTRA experienced ED visits in the year after medication dispensing. However, 8% of subject whose ICS was filled required oral corticosteroids compared with 11% of patients whose ICS-LABA and LTRA was filled (overall $P < .001$).

Adherence

To broadly assess adherence to the controller medications, we examined the number of refills after the initial fill. In TennCare Medicaid, 40% of the subjects who initiated ICS had no refills during the following 12 months, 33% of the subjects who initiated LTRA had no refills, and 46% of the subjects who initiated ICS-LABA had no refills. In the health plans, 50% of the subjects who initiated ICS had no refills compared with 35% who initiated LTRA and 45% who initiated ICS-LABA.

Cox regression results

Subjects with allergic rhinitis.—The results for subjects for the covariate adjustment and the hdPS adjustment were similar; thus, we present only the results that include hdPS. The fact that 2 different means of adjustment led to the same results supports the consistency of our findings. The results for subjects with or without a diagnosis of allergic rhinitis are presented in Table III. In the TennCare Medicaid population, the results were not significantly different for subjects treated with LTRA compared with subjects treated with ICS for the outcomes of receiving oral corticosteroids (hazard ratio [HR] 0.64 [95% CI, 0.34–1.22]), and experiencing a hospitalization (HR 1.88 [95% CI, 0.19–18.8]). For patients with a diagnosis of allergic rhinitis, the subjects in TennCare Medicaid who were treated with LTRAs were less likely to experience ED visits (HR 0.44 [95% CI, 0.21–0.93])

compared with subjects treated with ICS. The results were not statistically different between subjects treated with ICS-LABA and the subjects treated with ICS for the outcome of asthma-related ED visits (HR 0.72 [95% CI, 0.16–3.20]).

In the health plans, subjects treated with LTRA were not statistically different from subjects treated with ICS who experienced asthma-related ED visits (HR 1.26 [95% CI, 0.50–3.20]) and who required oral corticosteroids (HR 0.77 [95% CI, 0.35–1.72]). The Cox regression model for the outcomes of asthma-related hospitalizations in the health plan populations failed to converge, likely because relatively few subjects experienced hospitalizations. The subjects treated with ICS-LABA were not statistically different from subjects treated with ICS in experiencing asthma-related ED visits (HR 0.92 [95% CI, 0.11–7.55]) and requiring oral corticosteroids (HR 1.29 [95% CI, 0.38–4.34]).

For subjects without allergic rhinitis

Subjects treated with either LTRA or ICS-LABA without a diagnosis of allergic rhinitis in TennCare and the health plans were not statistically different in experiencing asthma-related hospitalizations or ED visits, or for the need of oral corticosteroids as subjects treated with ICS.

DISCUSSION

Our study has 4 key findings. First, although LTRAs have worse efficacy than ICS in clinical trials, children who initiated LTRAs in our real-life populations had similar outcomes as ICS users. Similarly, although results of clinical trials indicate that ICS-LABAs are superior to ICS alone or that ICS-LABAs help reduce the dose of ICS, we found that ICS users in real-life settings had similar outcomes as did ICS-LABA users in terms of subsequent asthma-related ED visits, hospitalizations, or dispensings of oral corticosteroids. Second, adherence to controller medications for asthma was generally poor because many subjects did not refill controller medications regardless of drug type, and adherence to ICS was worse than adherence to LTRAs. Third, children in the TennCare Medicaid population were more likely to be started on an LTRA rather than an ICS compared with the health plan populations. Fourth, children who had a diagnosis of allergic rhinitis and who were treated with LTRA in TennCare Medicaid were less likely to visit the ED for their asthma.

Contrary to the results of such randomized clinical trials, we did not find that the subjects who used ICS experienced fewer asthma-related exacerbations than subjects who used LTRA. Results of previous randomized clinical trials found greater efficacy of ICS compared with LTRA in children.^{27,28} Results of some studies also indicated that adults with randomized mild persistent asthma experienced greater efficacy, even with poorer adherence to ICS compared with LTRAs.^{29,30} One possible reason that our findings conflict with previous clinical trials is that LTRAs are just as effective as ICS in preventing asthma-related exacerbations in real-life settings. An alternative explanation for these results is unmeasured confounding. At baseline, the subjects who initiated LTRAs had less-severe asthma as in the previous 12 months, they experienced fewer hospitalizations, ED visits, and prescriptions for oral corticosteroids. We attempted to adjust for confounding with several measures, including counting the number of generic medications used in the prior year, the

Charlson comorbidity index, and the hdPS to account for baseline confounding. However, if LTRA users had less-severe asthma that was not measured by these variables, then this confounding could explain our results.

Our findings are consistent with results of other studies that indicated that a controller medication that is most efficacious in clinical trials might not be the most effective medication in real-life populations. Price et al³¹ studied the outcome of asthma quality of life and found that LTRAs may be equivalent to ICS as first-line controller therapies in patients with asthma after 2 months of therapy but not at 2 years. Ducharme et al³² compared ICS with LTRAs with 227 children and found that monotherapy with ICS did not significantly reduce the need for rescue oral corticosteroids or acute care visits. The investigators found that ICS were associated with a higher rate of hospitalizations but concluded that this finding could have been secondary to residual unmeasured confounding because subjects who were started on ICS were more likely to experience exacerbations. Results of a study by Bukstein et al³³ indicated that oral montelukast and inhaled fluticasone may have similar effectiveness in real-life populations because of greater adherence to montelukast. Bukstein et al³³ had a relatively small sample size, of 104, and suggested that they had persistent unmeasured confounders and selection bias.

In our study, we also found that the subjects were more likely to be adherent to LTRAs than to ICS. This finding was consistent with other studies. Jones et al³⁴ who found that adherence to new-start monotherapy on LTRAs was 68%, to ICS was 34%, and to LABAs was 40%. Results of another study also found lower adherence for ICS but found that the subjects in the highest adherence categories had lower odds of an ED visit.³⁵ Results of extension studies of randomized controlled studies found that LTRAs are equally as efficacious as ICS, possibly because adherence is higher.^{36–38} Although, in our analyses, we adjusted for adherence by using PDC, it is plausible that the observed effectiveness of LTRAs was due, in part to increased, adherence. Furthermore, our results do not suggest that ICS are not efficacious if taken properly. The goal of our study was to assess the effectiveness of controller medications for asthma as currently prescribed across diverse regions and health systems.

A greater proportion of TennCare Medicaid subjects filled prescriptions for LTRAs compared with ICS, and dispensing of LTRAs was associated with fewer ED visits (14%) compared with ICS (21%) and ICS-LABA (17%) in this population. Reasons for higher use of LTRAs compared with ICS could not be assessed in this study, but differential asthma severity across the populations; parental preference, including parental concern about the potential adverse effects of ICS; parental or clinician perceived higher adherence with oral medications rather than inhaled medications; and easier administration of oral medication compared with inhaled may all play a role.¹³ In support of these reasons, of a survey of asthma providers conducted by Sawicki et al,³⁹ indicated that 47% of providers reported that they might prescribe LTRAs instead of ICS because LTRAs were easier for families to use, and 18% of providers reported parental concerns over ICS adverse effects. In addition, because we do not have prescribing information for these subjects, it also is possible that prescriptions for ICS and LTRA were differentially filled, although we believe that this is somewhat less likely to account for these differences. These results (Table II) are in contrast

to the 3 health plan populations that all had a similar proportion of exacerbations (6%), which suggests that the increased prescribing of LTRAs in Medicaid could be associated with decreased ED visits but for reasons that could not be assessed in this study. What is suggested by these data is that use of medications and effectiveness of medications may vary in different populations, something not adequately addressed in efficacy randomized controlled trials. Whether this relates to disease severity or medication adherence, preference, ease of use, and/or medication response could not be determined, but it remains an important finding.

In addition, we found that children with allergic rhinitis in TennCare Medicaid and who initiated an LTRA had a lower risk of ED visits for asthma. The decrease in ED visits in TennCare Medicaid of subjects treated with LTRA compared with subjects treated with ICS is suggested to occur in subjects who have asthma and allergic rhinitis (Table III). The difference with results between TennCare Medicaid and the health plans could be related to a relative increased adherence to oral LTRAs in the TennCare Medicaid population in which competing priorities are high or other factors. Thus, part of the greater real-world effectiveness of LTRA in the TennCare Medicaid population may be due to effective treatment of coexistent asthma and allergic rhinitis with LTRAs.

Strengths of our study include a diverse and large population, detailed measures of adherence, and the ability to control for a number of potential confounders. To our knowledge, this study is the largest to assess the effectiveness of controller medications for asthma in children. Furthermore, we assessed effectiveness relative to adherence levels because we dichotomized our time-varying adherence measure into ≥ 0.75 or <0.75 . Despite the strengths of our study, several caveats deserve mention. Furthermore, our findings in the TennCare Medicaid population that subjects with allergic rhinitis experienced improved outcomes on LTRAs could have been related to improved adherence with LTRAs because of increased effectiveness for nasal symptoms. In addition, adherence could be an explanation of our findings. The use of intermittent LTRAs also could be more effective than the use of intermittent ICS or ICS-LABA; however, we were unable to account for this potential difference.^{40,41} Moreover, we do not know whether ICS were being used with aerochambers, which could influence the effectiveness of ICS. In addition, we were unable to be certain that our population of subjects with asthma had persistent asthma because there are currently no good mechanisms for identifying persistent asthma by using electronic data alone. Nevertheless, our population that included subjects who experienced asthma-related exacerbations in the previous year represents a population that is likely to require controller medications. Next, we were unable to assess whether the asthma exacerbations were triggered by upper respiratory infections alone, given that LTRAs have been demonstrated to be as effective as ICS in patients with upper respiratory illness-triggered asthma.¹ Furthermore, residual confounding by indication, despite our efforts to minimize confounding, may contribute to our findings that LTRAs may be just as or more effective than ICS, and this is a limitation of our observational study. The results of a prospective randomized clinical trial of effectiveness would address this limitation. In addition, the CIs of many of our HRs were wide, which suggests a lack of precision of our results. We also did not assess how the duration of treatment with controller medications affected effectiveness because the results of a previous study indicated that ICS may be more

efficacious than LTRA in the first 6 months but not at 1 year. Finally, a limitation of our study is that our population was heterogeneous with respect to the subjects, the disease, and the response to medications. Although this may be considered a limitation in a traditional efficacy study, it is considered a strength in answering effectiveness questions because our results are more likely to be generalizable to diverse, real-life populations.

CONCLUSION

Children who initiated LTRA had similar risks of ED visits, hospitalizations, and the need for oral corticosteroids as children who initiated ICS. These findings may be explainable by LTRA having similar effectiveness as ICS in real-life usage, by residual confounding by indication, or by other unmeasured factors. Children who had a diagnosis of allergic rhinitis and who were initiated on LTRA had a lower risk of ED visits in a Medicaid population.

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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

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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.

TABLE I.

Baseline demographics by controller medication group (N = 26,191)

	TennCare Medicaid (n = 10,624)				Health plans (N = 15,567)			
	ICS, % (no.) (n = 4,022)	LTRA, % (no.) (n = 5,867)	ICS-LABA, % (no.) (n = 735)	P	ICS, % (no.) (n = 13,505)	LTRA, % (no.) (n = 1,286)	ICS-LABA, % (no.) (n = 776)	P
Sex				.082				.11
Girls	43 (1,724)	43 (2,512)	47 (346)		41 (5,479)	42 (535)	44 (343)	
Boys	57 (2,298)	57 (3,355)	53 (389)		59 (8,026)	58 (751)	56 (433)	
Site								<.001
HPHC					15 (2031)	39 (506)	30 (233)	
Health Partners					9 (1,240)	30 (387)	48 (370)	
KPNC, KPGA, KPNW					76 (10,234)	31 (393)	22 (173)	
Race and/or ethnicity				<.001				<.001
White	48 (1,942)	60 (3,494)	55 (406)		31 (4,139)	25 (325)	23 (177)	
Black	41 (1,656)	31 (1,840)	39 (287)		12 (1,579)	5 (65)	7 (54)	
Latino	5 (204)	4 (254)	2 (16)		16 (2,178)	6 (81)	3 (25)	
Asian	1 (31)	1 (48)	0.4 (3)		8 (1080)	4 (45)	3 (21)	
Other/missing	5 (189)	4 (231)	3 (23)		33 (4521)	60 (770)	64 (499)	
History of smoking exposure	1 (47)	1 (67)	3 (22)	<.001	3 (355)	1 (17)	3 (24)	.011
Experienced the following in the previous 1 y								
ED visit	42 (1,671)	34 (2,013)	42 (311)	<.001	24 (3,243)	19 (240)	24 (187)	<.001
Hospitalization	13 (511)	5 (285)	7 (52)	<.001	6 (766)	4 (48)	3 (25)	<.001
Outpatient visit	32 (1,301)	26 (1,519)	34 (253)	<.001	47 (6,323)	40 (516)	49 (383)	<.001
OCS burst				<.001			<.001	
0	21 (825)	16 (938)	22 (158)		14 (1,899)	8 (106)	11 (88)	
1	54 (2,183)	60 (3,546)	56 (408)		72 (9,745)	71 (919)	68 (528)	
2	25 (1,014)	24 (1,383)	23 (169)		14 (1,861)	68 (528)	21 (160)	
Allergic rhinitis	13 (538)	18 (1038)	15 (112)	<.001	19 (2,569)	40 (516)	28 (224)	<.001
Acute respiratory illness	70 (2,825)	77 (4,501)	66 (482)	<.001	70 (9,416)	76 (979)	70 (545)	<.001

HPHC, Harvard Pilgrim Health Care; KPGA, Kaiser Permanente Georgia; KPNC, Kaiser Permanente Northern California; KPNW, Kaiser Permanente Northwest; OCS, oral corticosteroid.

Outcome frequencies in the 12 months after dispensing the controller medication in a subset of subjects who were continuously enrolled for the 12 months after controller medication dispensing: the number of subjects who experienced 1 or more ED visits, hospitalizations, oral courses of oral corticosteroids

TABLE II.

Outcome	TennCare Medicaid (N = 7,804)				Health plans (N = 11,334)			
	ICS, % (no.)	ICS-LABA, % (no.)	LTRA, % (no.)	P	ICS, % (no.)	ICS-LABA, % (no.)	LTRA, % (no.)	P
ED visits	21 (581)	17 (109)	14 (622)	<.001	6 (568)	6(34)	6 (58)	.75
Hospitalizations	3 (80)	3 (16)	2 (97)	.21	1 (113)	1 (6)	1 (7)	.57
Oral corticosteroids	19 (542)	16 (98)	18 (775)	.032	8 (774)	11 (62)	11 (100)	<.001

TABLE III.

Results from the extended Cox regression with time-varying PDC measure of subjects with (1) asthma only and (2) asthma and allergic rhinitis; the results are presented of a model that adjusted for the hdPS; the outcomes are time to event (ED visit, hospitalization, oral corticosteroids, or composite exacerbations)

Outcome	Site	Asthma only		Asthma and allergic rhinitis	
		LTRA vs ICS, HR (95% CI)	ICS/LABA vs ICS, HR (95% CI)	LTRA vs ICS, HR (95% CI)	ICS/LABA vs ICS, HR (95% CI)
ED visits	Health plans	1.72 (0.91–3.24)	*	1.26 (0.50–3.20)	0.92 (0.11–7.55)
	TennCare	1.10 (0.74–1.62)	1.50 (0.74–3.04)	0.44 (0.21–0.93) [‡]	0.72 (0.16–3.20)
Hospitalizations	Health plans	0.75 (0.10–5.67)	*	*	*
	TennCare	0.89 (0.29–2.74)	2.43 (0.51–11.6)	1.88 (0.19–18.8)	*
Oral corticosteroids	Health plans	1.04 (0.56–1.93)	0.93 (0.13–6.66)	0.77 (0.35–1.72)	1.29 (0.38–4.34)
	TennCare	1.32 (0.88–1.98)	1.25 (0.53–2.91)	0.64 (0.34–1.22)	*
Composite exacerbations outcome [‡]	Health plans	1.26 (0.77–2.09)	0.89 (0.22–3.59)	0.90 (0.48–1.68)	1.92 (0.74–4.96)
	TennCare	1.26 (0.95–1.69)	1.79 (1.05–3.05) [‡]	0.54 (0.32–0.93) [‡]	0.39 (0.09–1.69)

* The extended Cox regression model did not converge.

[‡] Statistically significant.

[‡] One or more ED visits or hospitalizations, or the need for oral corticosteroids.