Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: A nested case-control study

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Background: The US Food and Drug Administration has issued safety alerts about leukotriene receptor–modifying agents and suicidality/suicide, but because these were based on case reports, there is controversy about the association.
Objective: We conducted a nested case-control study to determine the association between leukotriene-modifying agents (LTMAs) and attempted suicide among asthmatic children and young adults.
Methods: Cases and control subjects were from a cohort of asthmatic patients aged 5 to 24 years who were new users of LTMAs or other asthma medications. Data were from an insurance claims database. Cases were defined as those with a suicide attempt (SA) occurring after exposure to asthma medication. Control subjects were persons at risk and were selected by using incidence density sampling in a 10:1 match. Conditional logistic regression was used to determine the association between LTMA exposure and the risk of attempted suicide adjusted for important covariates.
Results: We identified 344 cases and 3438 matched control subjects. Cases were more likely than control subjects to have risk factors for suicide. We found that current use of any LTMA was not associated with increased risk of an SA; in fact, the direction of effect was the opposite (adjusted odd ratio, 0.70; 95% CI, 0.36-1.39).
Conclusion: In this analysis we found that use of LTMAs was not associated with an increased risk of SAs in children, adolescents, and young adults with asthma. Further research needs to be conducted to more fully understand the association between LTMAs and suicide, particularly in subpopulations.
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Key words: *Asthma, suicide, leukotriene-modifying agents, montelukast, drug safety*

Abbreviations used
ED: Emergency department
FDA: US Food and Drug Administration
ICD-9-CM: International Classification of Diseases–Ninth Revision–Clinical Modification
LTMA: Leukotriene-modifying agent
MPR: Medication possession ratio
OR: Odds ratio
SA: Suicide attempt

Asthma, one of the most common chronic conditions in the United States, is a respiratory disorder characterized by airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. The disease affects approximately 24 million Americans, including 7 million children.[1,2] Asthma exacerbations can result in lost days of work and school, reduced quality of life, avoidable emergency department (ED) visits, hospitalizations, and death.

Treatment guidelines for asthma have been published by the National Heart, Lung, and Blood Institute that encourage stepwise therapy based on disease severity.[3] Several classes of medication are available for long-term control of asthma. Although inhaled corticosteroids are often used first, leukotriene-modifying agents (LTMAs) are an effective alternative.[3,4] These drugs, which in the United States include montelukast (Singulair; Merck & Co, Inc, Whitehouse Station, NJ), zafirlukast (Accolate; AstraZeneca Pharmaceuticals, Wilmington, NC), and zileuton (Zyflo; Cornerstone Therapeutics, Inc, Cary, NC), are administered orally and therefore are particularly useful in children. LTMAs work by preventing the inflammatory effects of leukotrienes, and all 3 are approved for asthma (montelukast is also approved for allergic rhinitis) and have been available in the United States since the late 1990s.[5] Among the LTMAs, montelukast is the most popular; in fact, the brand product, Singulair, has been among the top 10 best-selling drugs in the United States for several years.[6] Until recently, the LTMAs were considered to have minimal safety issues.

Beginning in 2008, when the US Food and Drug Administration (FDA) first issued a safety alert, there has been concern of a potential association between LTMAs and increased risk of suicide.[7] An FDA review of adverse event data from manufacturer-conducted placebo-controlled clinical trials found no association with suicide; nevertheless, subsequent communications by the FDA warned that "patients and prescribers should monitor for the possibility of neuropsychiatric events associated with these agents."[8] In June 2009, the FDA requested that manufacturers include a precaution in the drug-prescribing information for all LTMAs.[9] Although the number of suicide-related events related to LTMAs

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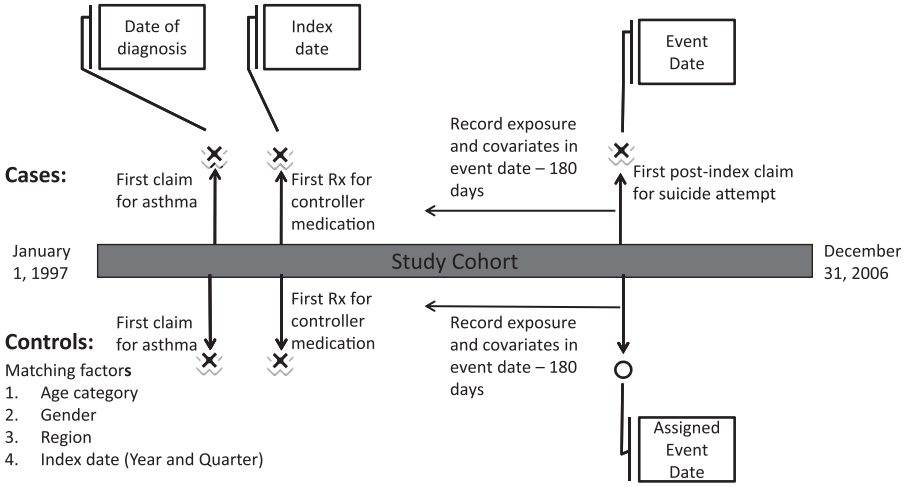

FIG 1. Nested case-control study design. Ten control subjects were matched with each case.

reported to the FDA have increased since 2008, it is unclear whether such reports are a result of the FDA warning or represent a true association.[10] Ecologic studies have failed to find an association,[11,12] and the only observational study that has been conducted was limited by small sample size and failure to include a comparison group.[13] Nevertheless, prescribing of LTMAs has decreased by 8.9% from 2007 to 2009.[11]

More objective information is needed about the potential association between LTMAs and suicide, particularly in children in whom LTMAs might be a preferential treatment option because of difficulty using inhalers. The purpose of this study was to assess the association between LTMAs and suicide attempts (SAs) in children, adolescents, and young adults with asthma.

METHODS

We conducted a case-control study of the association between the LTMAs and attempted suicides. Cases and control subjects were nested within a cohort of asthmatic children and young adults identified in a commercial health insurance claims database who were new users of LTMAs or other asthma medications, as shown in Fig 1.

Data source and cohort

The data for this study were obtained from the LifeLink Health Plan Claims Database (IMS Health, Inc, Danbury, Conn). The Lifelink Health Plan Database includes adjudicated medical and pharmaceutical claims along with demographic information (eg, age, sex, and geographic region) and dates of enrollment for more than 60 million unique anonymous patients from more than 90 health plans across the United States and is representative of the national commercially insured population on a variety of demographic measures. The data extract contained claims for patients with a diagnosis of asthma based on International Classification of Diseases–Ninth Revision–Clinical Modification (ICD-9-CM) codes of 493.XX whose age was between 5 and 24 years on at least 1 claim. Our analysis was restricted to patients with claims adjudicated between January 1, 1997, and December 31, 2006. This end date was selected to limit the potential for confounding by indication. Although the first FDA warnings about a potential association between LTMAs and suicide occurred in 2008, the package insert for Singular was changed to include a warning about suicidal thinking a year earlier and could have influenced prescribing thereafter.[7]

The cohort was limited to those patients with at least 1 prescription claim for an asthma controller medication, which included inhaled corticosteroids, LTMAs, long-acting β-agonists, methylxanthines, immunomodulators, mast cell stabilizers, and inhaled anticholinergics, and the date of the first claim for an asthma controller medication was defined as the index date. Because LTMAs are used for indications other than asthma, such as allergic rhinitis, or for off-label indications, patients were excluded if the index date occurred more than 30 days before the asthma diagnosis date. This was done to ensure homogeneity within the cohort with respect to suicide risk because asthmatic patients have a higher baseline risk of suicide. Patients were also excluded if they were less than 5 or greater than 24 years old on their index date or if their last enrollment date (ie, enrollment in the health plan) was on or before their index date. The latter was considered necessary for accurate assessment of exposure. Finally, subjects were excluded if they were not continuously enrolled for at least 6 months before the index prescription date or if they had significant gaps in enrollment in either the preindex or follow-up periods. Significant gaps were defined as 2 or more months of continuous disenrollment and 20% or more of total months.

Patients were followed until (1) an SA occurred, (2) disenrollment from the database, or (3) the end of the follow-up period (December 31, 2006).

Cases and control subjects

Cases were defined as those with an SA occurring after (at least 1 day) the index date. The ICD-9-CM codes used to identify SAs were E950 to E959, with subcategories of E950 to E952 (self-inflicted poisoning), E953 (self-inflicted injury by hanging), E954 (drowning), E955 (self-inflicted injury by firearms), E956 (self-inflicted injury by cutting), E957 (self-inflicted injury by jumping from high places), E958 (other/unspecified self-inflicted injury), and E959 (late effects of self-inflicted injury).

Potential control subjects were persons at risk for an event on the date of an event in a corresponding case. The study was planned to randomly select 10 control subjects from the at-risk population after matching to each case on (1) age (within groups 5-11, 12-18, and 19-24 years), (2) sex, (3) geographic region of the country (East, Midwest, South, and West), and (4) cohort entry quarter and year by using the incidence density sampling approach (without replacement) and assigned the "event" date of the case. Cases could serve as control subjects for other cases in the time period before the event. The choice of a 10:1 match was based on previous evidence that suggests that matching beyond 10 control subjects does not significantly increase statistical power.[14]

Exposure

LTMA exposure was determined in the 180 days before the event date (ie, date of SA in cases and corresponding date in control subjects). We first determined the exposed period for each prescription based on the prescription fill date and the number of days supplied as recorded in prescription claims.