Leukotriene Modifier Use and Asthma Severity

How Is a New Medication Being Used by Adults With Asthma?

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Background: The introduction of leukotriene modifiers, the first novel class of medications for asthma in more than 2 decades, provides an opportunity to evaluate the clinical context in which patients receive new treatments. Because milder asthma is usually controllable with more familiar medications, we hypothesized that adults with asthma would receive leukotriene modifiers for more severe disease.

Methods: We conducted a prospective, longitudinal, 18-month cohort study of 349 patients with asthma. We evaluated the association of baseline self-reported medication use and measures of asthma severity. We also examined the impact of baseline measurement of asthma severity on incident leukotriene modifier use at follow-up.

Results: At baseline, 39 (11%) of 349 patients reported leukotriene modifier use during the previous 2 weeks (95% confidence interval [CI], 8%-15%). Adults with asthma who reported recent use of leukotriene modifiers were more likely to indicate use of other long-term controller medications for asthma, such as inhaled corticosteroids (80% vs 57%; P = .007). Leukotriene modifier use was also associated with poorer severity-of-asthma scores (mean score difference, 3.6 points; 95% CI, 1.7-5.2 points) and asthma-specific health-related quality of life (mean score difference, 8.1 points; 95% CI, 3.4-12.8 points). Leukotriene modifier users were also more likely to indicate a recent emergency department visit (odds ratio [OR], 2.3; 95% CI, 0.9-5.6) or hospitalization for asthma (OR, 4.1; 95% CI, 1.4-11.4). Greater baseline asthma severity was associated with an increased probability of new-onset leukotriene modifier use during 18-month follow-up. Poorer baseline severity-of-asthma scores and asthma-specific quality-of-life scores were related to a greater likelihood of leukotriene modifier use at follow-up (OR per SD-sized score increment, 2.0; 95% CI, 1.4-2.7; OR, 1.8; 95% CI, 1.3-2.5; respectively). Recent hospitalization for asthma at baseline was also associated with a greater likelihood of leukotriene modifier use at follow-up (OR, 4.9; 95% CI, 1.6-14.8).

Conclusions: Adults with asthma who receive leukotriene modifiers have more severe asthma.

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The introduction of leukotriene modifiers, the first novel class of medications for the treatment of asthma in more than 2 decades, provides an opportunity to evaluate the clinical context in which patients receive new pharmacologic therapy for a chronic disease. Despite the recent emphasis on evidence-based medicine, it remains unclear how clinical trial evidence and practice guidelines are being translated into the actual treatments that patients receive.

The initial randomized placebo-controlled trials established the clinical efficacy of leukotriene modifiers in mild-to-moderate asthma. Based on several of these randomized controlled trials, the National Asthma Education and Prevention Program (NAEPP) 1997 treatment guidelines included leukotriene modifiers as an alternative to inhaled corticosteroids for the treatment of mild persistent asthma. These guidelines, however, did not address the use of leukotriene modifiers for more severe asthma or as combination therapy with inhaled corticosteroids.

Although the initial clinical evidence for leukotriene use focused on mild-to-moderate asthma, the spectrum of asthma severity is broader in clinical practice. Because inhaled corticosteroids are the usual first-line controller therapy for asthma, we hypothesized that adults with asthma who receive leukotriene modifiers would have more severe disease.

Methods

Study Design and Patient Recruitment

The study involved a prospective, longitudinal cohort of 401 adult patients with asthma...
recruited from physician practices in northern California. The University of California, San Francisco, Committee on Human Research approved the study. Details of recruitment and initial follow-up have been previously reported. \(^\text{12,14,16}\) In brief, beginning in 1993-1994, we initially recruited adults aged 18 to 50 years with asthma from a random sample of board-certified pulmonary specialists, allergists/immunology specialists, and family practitioners in northern California. Each participating physician maintained a registry of adults aged 18 to 50 years with outpatient visits for asthma during a prospective 4-week period. Physicians were instructed to include patients who met clinical diagnostic criteria for asthma and to exclude those with chronic bronchitis or emphysema. In the present study, we used baseline data from interviews conducted between July 1998 and December 1999 (study wave 4), with follow-up interviews 18 months later (wave 5). Of the 401 baseline respondents, 349 (87%) completed follow-up interviews and comprise the study cohort for this analysis. Each patient underwent structured, computer-assisted telephone interviews that assessed sociodemographic characteristics, medication use, self-reported asthma history, and health status.

### SELF-REPORTED MEDICATION USE

We evaluated medication use in a series of specific questions. For each medication, we listed all trade and generic names. For the inhaled medications, patients indicated whether they had used the medication during the past 18 months and past 2 weeks. The baseline questionnaire ascertained whether patients had used zileuton (Zyflar; Abbott Laboratories, Abbott Park, Ill) and zafirlukast (Accolate; AstraZeneca Pharmaceuticals, Wilmington, Del) during the past 18 months and past 2 weeks. For the assessment at 18-month follow-up, we used the same interview format but ascertained leukotriene modifier use during the previous 2-week period only. Because montelukast was newly available at the time of follow-up, we also elicited use of montelukast sodium (Singular; Merck & Co Inc, Whitehorse Station, NJ) tablets during the previous 2 weeks. Because these medications act on the same inflammatory pathway, we analyzed leukotriene modifiers as a class of medications rather than focusing on individual agents.

### CLASSIFICATION OF ASTHMA SEVERITY

In the current study, we examined the relationship between asthma severity and self-reported leukotriene modifier use. To assess asthma severity, we used a multifaceted approach that included a validated severity-of-asthma score, use of long-term controller medications (inhaled corticosteroids, long-acting inhaled \(\beta\)-agonists, methylxanthines, and oral corticosteroids), health-related quality-of-life (HRQL) assessment, and health care utilization for asthma. Conceptually, we reasoned that these measures reflect different aspects of asthma severity and health status.

We measured severity of asthma with a previously developed and validated 13-item, disease-specific severity-of-asthma score based on frequency of current asthma symptoms (daytime or nocturnal), use of systemic corticosteroids, use of other asthma medications (besides systemic corticosteroids), and history of hospitalizations and intubations. \(^\text{12,14,17}\) Of note, the validated severity-of-asthma score was developed before leukotriene modifiers were available and does not include them. Possible total scores range from 0 to 28, with higher scores reflecting more severe asthma.

In addition to the overall severity-of-asthma score, we evaluated the use of specific medication groups classified in the NAEP guidelines as long-term "controller medications." \(^\text{30}\) These included inhaled corticosteroids, long-acting inhaled \(\beta\)-agonists, methylxanthines, and oral corticosteroids.

We assessed self-perceived asthma severity, a construct delineated by Janson and colleagues, \(^\text{29}\) with the following question, "Do you believe that your asthma is severe, moderate, or mild?" Previous studies show that a greater self-perceived asthma severity correlates with increased clinical asthma severity, poorer psychological status, lower life satisfaction, and increased use of emergency department services for asthma.

The impact of asthma severity was further quantified using both disease-specific and generic HRQL measurements. We assessed asthma-specific quality of life using the Marks Asthma Quality of Life Questionnaire (AQLQ), a 20-item questionnaire that measures the physical, emotional, and social impact of asthma. \(^\text{39}\) Previous work demonstrates the validity of AQLQ and responsiveness to change in asthma status. \(^\text{20,21}\) Higher scores represent poorer asthma-specific quality of life. Generic physical HRQL was measured using the 12-Item Short-Form Health Survey (SF-12) questionnaire. \(^\text{22}\) The physical component summary score, which was defined from the original 8 subscales of the 36-Item Short-Form Health Survey by factor analysis, measures an underlying physical dimension of health. \(^\text{23}\) Previous work demonstrates the SF-12 instrument's validity in adult asthma. \(^\text{24}\) Higher scores reflect more favorable health states.

Finally, we used a utilization-based measure of asthma severity, based on self-reported urgent or emergent health care used for asthma. Interviews ascertained urgent or emergent medical care for asthma during the previous 12 months. Although patients could indicate more than one event in each category, we analyzed binary variables (\(\geq 1\) visit or hospitalization).

### STATISTICAL ANALYSIS

Interview data were analyzed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC). For bivariate comparisons, we used the \(t\) test (2-tailed, unpaired) for continuous variables and the \(\chi^2\) test for categorical variables. We examined the association between baseline leukotriene modifier use and measures of asthma severity: severity-of-asthma score, use of controller medications, self-assessed asthma severity, HRQL, and health care utilization for asthma. Using multivariate analysis, we controlled for patient characteristics that could confound the relationship between asthma severity and leukotriene modifier use. These factors, which were defined a priori, included demographic factors (age, sex, and race/ethnicity), measures of socioeconomic status (household income and educational attainment), and smoking history (ever vs never). We used multivariate logistic regression for dichotomous outcomes and multivariate linear regression for continuous outcomes.

We also examined the prospective impact of baseline measures of asthma severity on the subsequent incidence of leukotriene modifier use at 18-month follow-up. This analysis was restricted to the 310 patients who reported no leukotriene modifier use during the past 2 weeks at baseline interview. Multivariate logistic regression analysis was used to elucidate the association between each baseline variable and the use of leukotriene modifiers at 18-month follow-up, controlling for the same covariates.

Among the 310 patients without baseline leukotriene modifier use at baseline, we evaluated the impact of asthma specialty care on the incidence of leukotriene modifier use. Based on interview responses, we defined asthma specialty care as that provided by a primary physician whose specialty is allergy or pulmonary medicine or other ambulatory visits, such as consultations, to an allergist or a pulmonologist. To examine the
Of 349 adults with asthma, 39 (11%) reported leukotriene modifier use during the previous 2 weeks at baseline interview (95% confidence interval [CI], 8%-15%) (Table 1). These patients had used zileuton (6 patients), zafirlukast (32 patients), or both (1 patient). Leukotriene modifier users were slightly older, had lower educational attainment, and were more likely to indicate white, non-Hispanic race/ethnicity. Compared with nonusers, adults with asthma who recently used leukotriene modifiers were similar in sex and income level. Although there was no statistical difference in smoking status overall, leukotriene modifier users were less likely to indicate current smoking.

At baseline interview, adults with asthma who reported recent use of leukotriene modifiers were more likely to indicate use of other long-term controller medications for asthma (Table 2). In particular, recent inhaled corticosteroid use was more common among leukotriene modifier users (80%) compared with nonusers (57%; P = .007). In addition, recent long-acting inhaled β-agonist use was more frequent among the leukotriene modifier users compared with nonusers (51% vs 24%; P < .001). In the leukotriene modifier group, oral corticosteroid use during the past 18 months was more common among the leukotriene modifier users (79%) than among nonusers (39%; P < .001).

Leukotriene modifier use was also associated with greater asthma severity, controlling for personal characteristics (Table 3). Leukotriene modifier users had poorer mean severity-of-asthma scores (adjusted mean difference, 3.6 points; 95% CI, 1.7-5.2 points) and asthma-specific quality-of-life scores (adjusted mean difference, 8.1 points; 95% CI, 3.4-12.8 points). Adults with asthma who reported recent leukotriene modifier use also had worse generic physical HRQL scores, although the CI did not exclude “no difference.” When asked to rate severity of asthma, patients who used leukotriene modifiers were more likely to rate their asthma as “moderate” or “severe” compared with those who did not indicate leukotriene use.

In multivariate logistic regression analysis, users of leukotriene modifiers had greater utilization-based asthma severity (Table 3). Leukotriene modifier users were more likely to report recent urgent ambulatory asthma care visits. In addition, leukotriene modifier users were more likely to have had emergency department visits (odds ratio [OR], 2.3; 95% CI, 0.9-5.6) and hospitalization for asthma (OR, 4.1; 95% CI, 1.4-11.4) during the previous 12 months.

At 18-month follow-up, we reevaluated recent use of leukotriene modifiers (previous 2 weeks). Of the 349 patients at follow-up, 64 (18%; 95% CI, 14%-23%) reported using leukotriene modifiers during the previous 2 weeks. These patients had used zileuton (2 patients), zafirlukast (20 patients), montelukast (40 patients), or some combination (2 patients). Compared with baseline status, 37 patients (11%) were new users of leukotriene modifiers. Of the 39 patients who reported leukotriene modifier use at baseline, 27 (69%) continued to report use, and the remaining 12 (31%) had stopped using leukotriene modifiers.

We examined the impact of baseline asthma severity on new-onset leukotriene modifier use at follow-up among the 310 patients who indicated no baseline use, controlling for personal characteristics and smoking history (Table 4). Baseline use of inhaled corticoste-
roids was associated with a greater likelihood of incident leukotriene modifier use at 18-month follow-up (OR, 4.5; 95% CI, 1.8-11.4). Baseline use of other long-term controller medications was also related to greater probability of incident leukotriene modifier use (Table 4). Poorer baseline severity-of-asthma scores and asthma-specific quality-of-life scores were related to a greater likelihood of leukotriene modifier use at follow-up (OR per SD-sized score increment, 2.0; 95% CI, 1.3-2.5; respectively). At baseline, patients who perceived their asthma as “moderate” or “severe” were also more likely to report leukotriene modifier use at 18-month follow-up (OR, 2.6; 95% CI, 1.3-5.5). Recent asthma-related health care utilization at baseline interview was also related to a greater probability of leukotriene modifier use at follow-up. In particular, recent hospitalization for asthma at baseline was strongly associated with incident leukotriene modifier use (OR, 4.9; 95% CI, 1.6-14.8).

Specialist physician care for asthma was related to the likelihood of new-onset leukotriene modifier use at longitudinal follow-up. During the follow-up period, a substantial proportion of adults with asthma received asthma specialty care from a pulmonologist (n=96; 31%) or an allergist (n=37; 12%). Compared with patients who received ambulatory care from an internist, family practitioner, or general practitioner, treatment by a pulmonologist (OR, 2.7; 95% CI, 1.1-6.5) or an allergist (OR, 4.4; 95% CI, 1.5-12.4) was associated with a greater likelihood of new-onset leukotriene modifier use at follow-up interview, controlling for sociodemographic and smoking covariates. Controlling for severity-of-asthma score did not appreciably affect these results (data not shown). In contrast, there was no impact of health maintenance organization membership (n=205; 66%) on the likelihood of incident leukotriene modifier use (OR, 0.87 for health maintenance organization vs other insurance types; 95% CI, 0.41-1.8).

Table 3. Asthma Severity and Recent Leukotriene Modifier Use

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Recent LM Use (n=310)</th>
<th>Recent LM Use (n=39)</th>
<th>Bivariate P Value</th>
<th>Mean Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity-of-asthma score, ean (SD)</td>
<td>9.0 (5.4)</td>
<td>13.1 (6.0)</td>
<td>&lt;.001</td>
<td>3.6 (1.7 to 5.2)</td>
</tr>
<tr>
<td>Asthma-specific HRQL score, mean (SD)</td>
<td>15.3 (13.9)</td>
<td>25.2 (16.8)</td>
<td>&lt;.001</td>
<td>8.1 (3.4 to 12.8)</td>
</tr>
<tr>
<td>Generic physical HRQL, mean (SD)</td>
<td>46.1 (11.4)</td>
<td>42.2 (11.4)</td>
<td>.046</td>
<td>-1.9 (-5.6 to 1.7)</td>
</tr>
<tr>
<td>Self-rated severity, moderate or severe, No. (%)</td>
<td>142 (46)</td>
<td>30 (77)</td>
<td>&lt;.001</td>
<td>3.3 (1.5 to 7.4)†</td>
</tr>
<tr>
<td>Urgent ambulatory visit (&gt;1 visit), No. (%)</td>
<td>89 (29)</td>
<td>22 (56)</td>
<td>&lt;.001</td>
<td>3.1 (1.5 to 6.4)†</td>
</tr>
<tr>
<td>Emergency department visit (&gt;1 visit), No. (%)</td>
<td>45 (15)</td>
<td>9 (23)</td>
<td>.16</td>
<td>2.3 (0.9 to 5.6)†</td>
</tr>
<tr>
<td>Hospitalization (&gt;1 visit), No. (%)</td>
<td>17 (6)</td>
<td>8 (21)</td>
<td>&lt;.001</td>
<td>4.1 (1.4 to 11.4)†</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HRQL, health-related quality of life; LM, leukotriene modifier; OR, odds ratio.
*Recent LM users vs nonusers controlling for age, sex, race, smoking status, income, and education.
†OR (95% CI).

Table 4. The Longitudinal Impact of Baseline Asthma Severity on Incident Leukotriene Modifier Use at 18-Month Follow-up (Among 310 Previous Nonusers)

<table>
<thead>
<tr>
<th>Measure of Asthma Status at Baseline</th>
<th>Likelihood of LM Use at 18-Month Follow-up, OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline medication-based asthma severity</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroid use in past 2 wk</td>
<td>4.5 (1.8-11.4)</td>
</tr>
<tr>
<td>Long-acting inhaled β-agonist in past 2 wk</td>
<td>4.9 (2.4-10.2)</td>
</tr>
<tr>
<td>Both inhaled corticosteroid and long-acting inhaled β-agonist use</td>
<td>4.3 (2.1-9.0)</td>
</tr>
<tr>
<td>Oral corticosteroid use</td>
<td></td>
</tr>
<tr>
<td>Any use during past 18 mo</td>
<td>1.9 (0.9-3.8)</td>
</tr>
<tr>
<td>Any use during past 2 wk</td>
<td>2.9 (1.3-6.8)</td>
</tr>
<tr>
<td>Steroid dependent†</td>
<td>2.4 (0.94-5.9)</td>
</tr>
<tr>
<td>Baseline asthma severity or health status</td>
<td></td>
</tr>
<tr>
<td>Asthma-specific HRQL score‡</td>
<td>1.8 (1.3-2.5)</td>
</tr>
<tr>
<td>Generic physical HRQL score‡</td>
<td>1.5 (1.04-2.2)</td>
</tr>
<tr>
<td>Self-rated severity, moderate or severe</td>
<td>2.6 (1.3-5.5)</td>
</tr>
<tr>
<td>Severity-of-asthma score‡</td>
<td>2.0 (1.4-2.7)</td>
</tr>
<tr>
<td>Baseline utilization-based asthma severity</td>
<td></td>
</tr>
<tr>
<td>Urgent ambulatory visit (&gt;1 visit in past 12 mo)</td>
<td>3.3 (1.5-6.9)</td>
</tr>
<tr>
<td>Emergency department visit (&gt;1 visit in past 12 mo)</td>
<td>2.3 (0.96-5.6)</td>
</tr>
<tr>
<td>Hospitalization (&gt;1 visit in past 12 mo)</td>
<td>4.9 (1.6-14.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HRQL, health-related quality of life; LM, leukotriene modifier; OR, odds ratio.
*Controlling for age, sex, race, smoking status, income, and education.
†Steroid dependent is defined as the use of prednisone or another steroid pill at least 2 times a week for at least 3 months in the previous year.
‡Per standard deviation–sized score increment (severity-of-asthma score and asthma-specific quality-of-life score) or decrement (generic physical HRQL score).
Leukotriene modifiers represent the first major new medication for the treatment of asthma in more than 2 decades. The most widely accepted guidelines in this country from the NAEPP supported their use as a long-term controller medication for mild persistent asthma as an alternative to inhaled corticosteroids. However, the translation of these clinical trial results and practice guidelines into the actual treatments received by adults with asthma remains uncertain. In both baseline and longitudinal analysis, greater asthma severity was associated with leukotriene modifier use. As a consequence, it seems that leukotriene modifiers are being used to treat adults with more severe asthma, often as part of combination therapy.

Our findings offer insight into how a new medication may enter into clinical use, from the perspective of the end user. To the extent that self-reported medication use indirectly reflects the prescription patterns of health care providers, these results suggest that clinicians were prescribing leukotriene modifiers for more severe asthma, often as part of combination therapy. Because providers were probably more familiar with inhaled corticosteroids and other existing controller medications, they may have been more likely to prescribe these initially for milder asthma. The finding that leukotriene modifier use was more common among adults with greater asthma severity could reflect clinicians’ perceived need for treatment alternatives for severe asthma not controlled with conventional medications. This broader use of leukotriene modifiers suggests that health care providers may be extrapolating practice guidelines and clinical trial results to novel clinical situations, in this case to a more severe spectrum of disease.

Data collection for this analysis began in 1998, 1 year after the NAEPP guidelines for asthma were published. At that time, available data from controlled clinical trials of leukotriene modifiers were based on treatment of patients with mild-to-moderate asthma. Most of these trials were relatively small, were conducted for short periods, and used variable clinical end points (e.g., forced expiratory volume in 1 second, peak expiratory flow rate, and symptom scores). Since the guidelines were published and our data collection occurred, there have been several clinical trials demonstrating the efficacy of leukotriene modifiers as combination therapy with inhaled corticosteroids and in adults with severe asthma. Based on these trials, the NAEPP guidelines were updated in 2002 to include combination therapy with inhaled corticosteroids and leukotriene modifiers as 1 of 4 alternatives for the treatment of moderate persistent asthma. These recent data and revised guidelines, however, would not have been accessible to most clinicians during this study period.

Several limitations of this study should be taken into account when interpreting the results. The interviews ascertained self-reported medication use rather than interviewing health care providers or obtaining pharmacy dispensing data. As a consequence, our analysis focuses on the end user and only indirectly reflects clinicians’ prescribing behavior. The analysis cannot distinguish whether providers offered treatment with leukotriene modifiers or patients solicited it. Because prescription or pharmacy dispensing of medication may not always equal personal use of the medication, our approach has the advantage of measuring medication use, a patient-centered construct. The study also focused on leukotriene modifier use in the previous 2 weeks, which may not always reflect medication use during a longer period. Further analysis, however, indicated that results are similar when baseline leukotriene modifier use during the past 18 months was examined (data not shown). Importantly, this study examined the impact of asthma severity on leukotriene modifier use in a cohort of adults with asthma; the study was not designed to examine the effectiveness of leukotriene modifiers.

Although this study does not focus on the effectiveness of leukotriene modifiers, some comment on their role in asthma therapy is warranted. Leukotriene modifiers are an appropriate long-term controller medication for mild-to-moderate asthma. These medications, however, may be less effective than inhaled corticosteroids for the prevention of asthma exacerbations. In adults with moderate-to-severe asthma, leukotriene modifiers improve asthma control as part of combination therapy with inhaled corticosteroids. Leukotriene modifiers used at conventional doses, however, were not as effective as high-dose therapy. Future clinical trials should evaluate the optimal dosing of leukotriene modifiers when used as combination therapy. In addition, studies are needed to compare addition of leukotriene modifiers to inhaled corticosteroids versus a higher dose of inhaled corticosteroids.

New therapeutic options for chronic diseases are being developed and introduced at a rapid rate. Clinical trials may not be available to address potentially important uses of new medications; practice guidelines may not always reflect rapidly changing medical knowledge. Consequently, new treatments may be used for patients who differ from the target group, as defined by randomized controlled trials, in clinically important ways. As in the case of leukotriene modifiers, the use of new therapies may extend beyond the available clinical evidence. These situations, when identified, suggest the need for further clinical trials or effectiveness analyses to address the areas of perceived clinical need.

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