Evaluation of the Utilization Patterns of Leukotriene Modifiers in a Large Managed Care Health Plan

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ABSTRACT

OBJECTIVE: To assess the utilization of leukotriene modifiers (LM) relative to national guidelines and to investigate possible emergency room utilization differences for LMs as monotherapy versus inhaled corticosteroid (ICS) monotherapy or combination ICS and LM therapy.

METHODS: The utilization of leukotriene modifiers (montelukast sodium, zafirlukast, and zileuton), concurrent inhaled steroids (beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone), beta-agonists (albuterol, bitolterol, formoterol, isoetharine, levalbuterol, metaproterenol, pirbuterol, salmeterol, and terbutaline) and low-sedating antihistamines (LSAs) cetirizine, desloratadine, fexofenadine, and loratadine) were assessed from the drug claims database of a large health insurer for dates of service for the 12-month period from September 1, 2001, through August 31, 2002. New-start LM patients were identified as having no previous LM drug claim within a 180-day look-back period from the first date of fill for the LM. Claims were stratified into age cohorts of "under 16 years" and "16 years and older." Emergency room (ER) claims for patients utilizing LMs, ICSs, and patients on both LM and ICS were retrieved for analysis from the medical claims database for the same 12-month study period.

RESULTS: More than 89% of new LM starts had no history of an ICS in the claims database. Overall, 61% of all (new and existing) LM patients did not have a claim for an ICS in their drug claims profile during the study period. An estimated 25% of LM utilization was not for asthma. No differences in ER utilization were found between ICS users and LM users; however, the ER utilization rate (0.090 ER visits per patient per year) was lower with combination therapy compared with monotherapy with ICS (0.110 ER visits per patient per year, $P = 0.001$) or LM (0.119 emergency room visits per patient per year, $P < 0.001$).

CONCLUSIONS: The majority of LM use in this health plan was initial monotherapy, contrary to national treatment guidelines for asthma. At the time of the study, the apparent off-label use of LM for allergic rhinitis was significant for this health plan.

KEYWORDS: Leukotriene modifiers, Inhaled steroids, Beta-agonists, Low-sedating antihistamines, Emergency room utilization

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Leukotriene modifiers (LM) include the 2 leukotriene receptor antagonists—zafirlukast (Accolate, approved by the FDA in September 1996) and montelukast sodium (Singulair, approved in February 1998)—and the leukotriene formation inhibitor zileuton (Zyflo, approved in January 1997).¹ The LM class of drugs was a new addition to the pharmacotherapy armamentarium in the treatment of asthma. Since 1996, the utilization of LMs has grown because of their ease of administration (including once-daily dosing) and some largely unsubstantiated concern among physicians and patients over the perceived adverse effects from the long-term use of corticosteroids. Numerous clinical studies have also shown that LMs, when compared with inhaled corticosteroids (ICSs) for the treatment of asthma, are associated with higher hospital event rates and asthma care costs and increased use of short-acting beta-agonists.²⁻⁴

There has been some supposition that the oral formulation of LMs will be associated with better compliance compared with the inhaled formulation of ICS agents.⁵ While there is some support for this in the literature, it has yet to be shown that greater adherence results in superior clinical outcomes.^{6,7} Sherman et al. found that, while compliance was better for LMs, it was suboptimal for both LMs and ICSs.⁷ Bukstein found, in a small study, statistically significant better compliance with LMs as compared with ICSs in mild asthmatic children; however, there was no difference in any outcome measure between the ICSs and LMs.⁸ More work is required to determine the extent to which clinical outcomes might be improved with increased LM compliance.

Better treatment outcomes with ICSs and no current evidence of compliance benefits associated with LMs supports the use of ICSs as the drugs of choice in the treatment of asthma.^{9,10} The National Asthma Education and Prevention Program Expert Panel Report (NAEPP EPR), sponsored by the National

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TABLE 1 NAEPP-EPR2 Goals of Asthma Therapy*

- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations.
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care

*National Asthma Education and Prevention Program (NAEPP) Expert Report sponsored by the National Heart, Lung, and Blood Institute (NHLBI). NAEPP EPR (Expert Panel Report)-2. The complete guidelines are available at: www.nhlbi.nih.gov/guidelines/asthma/index.htm.

Heart, Lung, and Blood Institute on the diagnosis and management of asthma, outlines 6 general goals of asthma therapy (Table 1) and provides a therapeutic algorithm designed to achieve these goals. The NAEPP EPR 2 in 1997 was issued shortly after the commercial availability of the first LM, zafirlukast. In 2002, an update to the NAEPP EPR 2 was released on selected topics. LMs were addressed in the update: "The LTRAs have been demonstrated to provide statistically significant but modest improvements in lung function when used as monotherapy in both adults and children. . . . When comparing overall efficacy of LTRAs to inhaled corticosteroids in adult patients with persistent asthma, most outcome measures significantly and clearly favored inhaled corticosteroids. . . ." The NAEPP EPR 2 was also modified to recommend LMs as an alternative but not preferred treatment to ICS when " . . . patient circumstances regarding administration of inhaled corticosteroids warrants selection of oral treatment"¹⁰ (see Figure 1, abstracted from <http://www.nhlbi.nih.gov/guidelines/asthma/execsumm.pdf>).

First approved in February 1998 for use in asthma, on December 31, 2002, montelukast sodium became the first LM to be approved by the U.S. Food and Drug Administration (FDA) for use in allergic rhinitis. The coincident movement of the leading low-sedating antihistamines ([LSA] loratadine, Claritin) to over-the-counter (OTC) status, beginning in the same month (December 2002), precipitated concern in our health plan about the potential for increased utilization of LMs as a prescription alternative to OTC loratadine. Currently, the role of LMs in the treatment of allergic rhinitis remains inconclusive. The new allergic rhinitis indication for montelukast was not approved for concomitant use with antihistamines.

Available clinical guidelines¹¹⁻¹³ for allergic rhinitis support the use of intranasal steroids as preferred therapy for moderate to severe allergic rhinitis. In addition, it has been shown that, in the treatment of seasonal allergic rhinitis, the clinical effects of the combination of an LM with an oral antihistamine are not significantly different from the use of an oral antihistamine alone.¹⁴ Studies have also shown that, in patients with seasonal allergic

rhinitis, intranasal steroids are more effective than an LM-anti-histamine combination for the reduction of pollen-induced nasal eosinophilic inflammation and for control of nasal symptoms.¹⁵

Objective

LMs were in the top 20 drug classes for cost during 2002 for our health plan and in the top 35 for prescription count; health plan costs had increased more than 13% in 2002 compared with the previous year. Due to the rise in utilization and costs and reports in the literature of possible emergency room (ER) visits precipitated by the drug therapy change from ICSs to LMs,¹⁶ our Drug Utilization Review (DUR) committee requested a review to assess the current utilization of LMs. The objective was to assess the utilization of LMs in the context of the current recommended guidelines for asthma and allergic rhinitis and to consider possible changes in formulary or tier copayment placement. A subanalysis was undertaken to assess possible differences in ER rates for those patients on ICS, LM, or both.

Methods

The prescription claims database for a 444,376-patient managed care organization in Upstate New York was used to examine utilization data for patients who received prescriptions for LMs zafirlukast, montelukast, and zileuton. Both new LM starts (defined as no claim in history 180 days prior to index date) and continued LM utilization between the dates of September 1, 2001, and August 31, 2002, were collected. The date of the first claim in history during the specified time frame served as the index date. Corresponding ER utilization was determined by the existence of medical claims with current procedural terminology (CPT) codes 99281 through 99285 (ER services for a new or established patient) for the same time frame (Figure 2).

Drug utilization was also grouped into 2 subsets: under age 16 years and age 16 years and older. New starts were further differentiated by the existence of an ICS (beclomethasone, budesonide, flunisolide, fluticasone, or triamcinolone) claim within 180 days prior to the start of the LM and those with an LSA (cetirizine, desloratadine, fexofenadine, or loratadine) in the claim history 180 days prior to the start of the LM. Total LM utilization was also differentiated by existence of an ICS, LSA, or beta-agonist (albuterol, bitolterol, formoterol, isoetharine, levalbuterol, metaproterenol, pirbuterol, salmeterol, or terbutaline) claim in the profile between September 1, 2001, and August 31, 2002. Rates and proportions were assessed for statistical significance using a test of homogeneity of proportions (chi-square goodness-of-fit test). Because of the large numbers, the data were assumed to be normally distributed.

Results

New Starts: Leukotriene Modifiers, Inhaled Steroids and Low-Sedating Antihistamine

In the population studied, 89.4% of new starts on LMs did not

FIGURE 1 Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years: Treatment

Classify Severity: Clinical Features Before Treatment or Adequate Control			Medications Required To Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	PEF or FEV ₁ PEF Variability	Daily Medications
Step 4 Severe Persistent	Continual Frequent	≤ 60% > 30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – High-dose inhaled corticosteroids AND – Long-acting inhaled beta₂-agonists AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	> 60% – < 80% > 30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Low-to-medium dose inhaled corticosteroids and long-acting inhaled beta₂-agonists. ■ Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range OR – Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. <p>If needed (particularly in patients with recurring severe exacerbations):</p> <ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range and add long-acting inhaled beta₂-agonists. ■ Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	≥ 80% 20–30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroids. ■ Alternative treatment (listed alphabetically): cromolyn, leukotriene modifier, nedocromil, OR sustained-release theophylline to serum concentration of 5–15 mcg/mL.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	≥ 80% < 20%	<ul style="list-style-type: none"> ■ No daily medication needed. ■ Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.
Quick Relief All Patients	<ul style="list-style-type: none"> ■ Short-acting bronchodilator: 2–4 puffs short-acting inhaled beta₂-agonists as needed for symptoms. ■ Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroids may be needed. ■ Use of short-acting beta₂-agonists >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.

Step down

Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.

Step up

If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled beta₂-agonist
- Minimal or no adverse effects from medications

Note

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is % of personal best; FEV₁ is % predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroids); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled beta₂-agonists. Overreliance on short-acting inhaled beta₂-agonists (e.g., use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy.
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if step 4 care is required. Referral may be considered if step 3 care is required.

TABLE 2 New Start Patients* on Leukotriene Modifiers (LMs)

Age Group	No. of Patients	No ICS† (180 Days Prior to Index Date)	With LSA‡ (180 Days Prior to Index Date)
		No. of Patients (%)	No. of Patients (%)
16 and over	1,174	1,081 (92.1)	258 (22.0)
Under 16	908	781 (86.0)§	266 (29.3)
Total	2,082	1,862 (89.4)	524 (25.2)

* New starts were defined as no LM claim in the preceding 180 days.

† ICS = inhaled corticosteroid.

‡ LSA = low-sedating antihistamine.

§ $P < 0.001$ for the comparison between the 2 age groups.

TABLE 3 Total Leukotriene Modifier Utilization

Drug	Patient Count Age 16 and Older	% of Total*	Patient Count Under Age 16	% of Total*
Zileuton 600 mg tab	38	0.76	0	0.00
Montelukast 10 mg tab	4,205	83.68	732	21.05
4 mg chew tab	2	0.04	804	23.12
5 mg chew tab	47	0.94	1,916	55.1
Zafirlukast 10 mg tab	18	0.36	10	0.29
20 mg tab	715	14.23	15	0.43
Total†	5,025		3,477	

* Totals may not equal 100% due to rounding.

† A patient could be counted twice, or more, if, during the observation period, the patient had claims for different agents (i.e., drug switches).

TABLE 4 Utilization of Inhaled Steroids, Low-Sedating Antihistamines and Beta-Agonists in Patients Receiving Leukotriene Modifiers

Age Group	No. of Patients	No Steroid Inhaler Claim in History (%)	With Low- Sedating Antihistamine Claim History (%)	Beta- Agonist Claim in History (%)
		No. of Patients	No. of Patients	No. of Patients
16 and older	4,968	3,105 (62.5)	2,045 (41.2)	3,718 (74.8)
Under 16	3,324	2,005 (60.3)	1,680 (50.5)	2,548 (76.7)
Total	8,292	5,110 (61.6)	3,725 (44.9)	6,266 (75.6)

have an ICS claim in their profile 180 days prior to the index date (Table 2). The percentage was higher in the age-16-years-and-older group (92.1%) than was found in the under-age-16-years cohort (86.0%, $P < 0.001$). This appeared to be contrary to anecdotal information received from committee physicians, where there was some concern regarding long-term steroid use in pediatric patients. Direct-to-consumer (DTC) advertising could play a role in greater use of LM in the age-16-years-and-older population, with adults possibly seeking the medication in response to an advertisement. Juvenile and pediatric populations are generally not the focus for this type of consumer advertising, though we have no data to corroborate this supposition of the effect of DTC advertising on LM utilization. These findings suggest that current prescribing practice for our health plan patients involves the use of LMs as initial maintenance therapy and not as add-on therapy to inhaled steroids.

LMs are not indicated for concomitant use with LSAs, and research has shown no additional benefit when combined with LSAs. Overall, 25.2% of new LM starts had existing or prior use of LSAs (defined as having a claim in history 180 days prior to index date). In the under-age-16-years group, there was a greater percentage of patients with existing LSA claims in history (29.3% versus 22.0%, $P < 0.001$). This finding was not unexpected. The occurrence of allergic rhinitis with asthma has been estimated at anywhere from 6.2% to 95% and has been shown to be an independent risk factor for asthma in adults.¹⁷ With the FDA approval of montelukast for allergic rhinitis, the potential for simplifying therapy by treating 2 different disease states with 1 medication may exist; however, the modest clinical benefit that LMs appear to have in both asthma and allergic rhinitis may limit this possibility. (Table 3 shows the distribution of LM utilization by drug and dose.)

For the total population of users of LMs, 61.6% did not have an inhaled steroid claim in their history during the 12-month study period. This would indicate that monotherapy with LMs is common. We did not investigate if an LM was being used concomitantly with long-acting beta-agonists.

The entire population of users of LM agents (both new starts and existing utilizers) were examined to identify the concomitant use of an ICS, LSA, or beta-agonist. Overall, 75.6% of patients with a claim for an LM did have a prescription filled for a long- or short-acting beta-agonist within the 12-month time frame of the observation period (Table 4). The existence of a beta-agonist claim for a patient was added as a proxy for a diagnosis of asthma. Standard of care for asthmatics includes the availability of an acute relief medication at all times. It was recognized that this is not a specific method of identifying the intended use for the medication. Mild-controlled asthmatics may not have the need for a beta-agonist prescription filled during a 12-month time frame. Also, beta-agonists are commonly used for acute, episodic care of upper respiratory infections and cough in nonasthmatic patients. While acknowledging the

FIGURE 2 Retrospective Analysis of Leukotriene Modifier Utilization From Pharmacy Claims and Emergency Room Admission Claims

* LM = leukotriene modifier.

† Members with a claim for a leukotriene modifier in their pharmacy claim history between the dates of 9/01/01 and 8/31/02 were stratified by age recorded with the last claim in history during the study period.

‡ Members with a claim for an inhaled corticosteroid in their pharmacy claim history between the dates of 9/01/01 and 8/31/02 were stratified by age recorded with the last claim in history during the study period. Members were then further stratified by the existence of a claim for an emergency room visit (CPT 99281– 99285) in the medical claim history from 9/01/01 to 8/31/02.

§ CPT = current procedural terminology.

TABLE 5 Emergency Room (ER) Visits in Users of Leukotriene Modifiers (LMs) and/or Inhaled Corticosteroids (ICSs)

	No. ER Visits	No. ER Patients	No. ER Visits/ER Patient	Total No. Patients	No. ER Visits/Patient
ICS monotherapy	1,089	793	1.37	9,886	0.110
LM monotherapy	608	455	1.34	5,110	0.119
ICS-LM dual therapy	286	209	1.37	3,182	0.090*

Data from claims dated 9/01/01 to 8/31/02, rates per 12 months.

* Statistically significant compared with either ICS ($P = 0.001$) or LM ($P < 0.001$) monotherapy.

inherent flaws in this measure, it is estimated that as much as 25% of current LM use could be for off-label utilization, i.e., allergic rhinitis.

This finding was used to support the implementation of a management strategy in which LM prescriptions required a tier-3 copayment unless the patient with the new LM claim had a prescription claim in history for an asthma medication. LM prescriptions were assigned a tier-2 copayment if the patient had received an asthma medication (short- or long-acting beta-agonist, ICS, or theophylline) within 6 months prior to the LM claim. Otherwise, the LM prescription claims would adjudicate at the higher, tier-3 copayment. This management strategy for LMs was endorsed by the DUR committee and was consistent with the placement of all prescription LSAs in the third (highest) copayment tier by the health plan. While this is not an exact mechanism of determining intended use for the LM agents, it was felt to be a reasonable administrative strategy and one that did not impose a burden on internal plan resources, participating physicians, or their staff.

Due to published findings of increased ER use and hospitalizations for asthma when switching from an ICS to an LM, overall ER use by drug class was evaluated.¹⁶ Patients were stratified into ICS monotherapy, LM monotherapy, or concomitant ICS-LM therapy. The ER visits were not specifically limited to an asthma diagnosis, and no adjustments for case or asthma severity were made.

There was no difference in occurrences of ER claims with monotherapy with LM or ICS ($P = 0.106$) (Table 5). Visits per ER patient and visits per patient were statistically similar among users of LM monotherapy and users of ICS monotherapy. ER utilization was lower (0.090 ER visits per patient per year) for combination therapy compared with either ICS monotherapy ($P = 0.001$) or LM monotherapy ($P < 0.001$).

Since these patients were not stratified by disease severity, we cannot speculate about the relative therapeutic value of LM versus ICS as measured by the incidence of ER visits. Differences in average case severity could influence the finding of apparent lower ER utilization by users of combination LM and ICS. If LMs are being used as initial monotherapy, it

could be argued that this group is more representative of mild-to-moderate asthmatics while the ICS users may be more representative of moderate-to-severe asthmatics. If there was significant off-label utilization of LMs for allergic rhinitis as we have supposed, this could also affect the findings, causing the utilization rate for LMs to appear to be artificially low since ER admissions due to allergic rhinitis occur rarely. The possible impact of this variable was not quantified in our study.

The statistically significant lower ER utilization rate for those patients taking combination LM and ICS is worth further exploration. It was assumed that this cohort would include severe asthmatics and therefore would have higher ER utilization; conversely, dual therapy could represent more aggressively treated patients and be the reason for the lower utilization rate and possible better outcome. Since we did not measure case severity, we cannot determine if this is true. This finding supports the need for further research into combination therapy with ICS and LM.

Limitations

Our investigation examined only utilization of 3 LM agents, ICSs, and LSAs. We did not investigate if an LM was being used concomitantly with long-acting beta-agonists. The long-acting beta-agonist controller medications could influence either the LM or ICS groups if use patterns differed between the groups. Second, the existence of a short-acting beta-agonist claim is an imperfect determinant of intended LM use for asthma, since, for example, beta-agonists are commonly prescribed for upper respiratory infections; this proxy method could therefore result in an overestimate of the use of LMs for asthma. However, this tendency to overestimate the use of LMs for asthma may be offset by the fact that not all asthmatics will obtain a refill prescription of their acute relief (short-acting beta-agonist) medication in a 12-month study period.

We also could not verify concurrent use of an LM and an LSA; we determined only that their use occurred in the same patient within a 180-day period. This may not be reflective of true concomitant use and, alternatively, could represent therapy failures when the patients switch from one drug to another.

The incidence of ER visits reported in our study may overstate the rate of ER visits attributable to asthma since we did not assess the diagnostic codes on the ER claims. However, unless there was an underlying, disproportionate amount of concomitant disease in one group versus another, any difference in ER utilization could conceivably be attributable to the disease (asthma) or its treatment. Differences in medication utilization were found in the age-16-years-and-above cohort versus the below-age-16-years cohort. Since the ER utilization was not separated into these 2 age groups, we could not determine if age influenced ER utilization and might possibly confound the apparent differences in ER utilization associated with drug use. Disease severity was also not assessed in the ER utilization analysis.

Conclusions

LMs in our population appear to be used commonly as initial therapy rather than as additional therapy to either reduce the dose of ICSs or improve asthma control. Utilization analysis showed possible significant use of LMs for indications other than asthma. Both findings are inconsistent with current clinical guidelines that recommend that ICS be used as first-line therapy (LM may be used as an alternative, add-on therapy). Our data did not show a significant difference in ER admission rates for ICS monotherapy versus LM monotherapy, but we did not adjust for disease severity. The ER utilization rate for patients on combination ICS and LM therapy was less than that for patients on therapy with either agent alone. The role of LMs and their place in therapy is evolving. Until the therapeutic role of LMs is better elucidated, these study findings will be used in our health plan to support intervention strategies and tier copayments to encourage the appropriate use of LMs, consistent with current evidence as manifest in clinical practice guidelines for both asthma and allergic rhinitis.

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