Published in final edited form as:

J Asthma. 2011 December ; 48(10): 1051–1057. doi:10.3109/02770903.2011.627488.

Risk Factors for Montelukast Treatment Failure in Step-Down Therapy for Controlled Asthma

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Abstract

Background—Leukotriene receptor antagonists including montelukast are an option for step-down therapy for mild asthmatics controlled on low-dose inhaled corticosteroids (ICS). Because some patients fail montelukast step-down therapy, it would be helpful for clinicians to be able to predict the risk of treatment failure.

Objectives—To determine patient characteristics associated with montelukast treatment failure and develop a clinical index to predict the risk of montelukast treatment failure.

Methods—Using the 165 participants in the Leukotriene or Corticosteroid or Corticosteroid-Salmeterol Study (LOCCS) trial who were stepped down from low-dose ICS to montelukast, we determined associations between enrollment variables and treatment failure. We constructed a montelukast failure index to predict the risk of montelukast treatment failure during step-down. To assess its specificity for montelukast, index performance was evaluated in the other LOCCS treatment groups.

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The authors report no conflicts of interest.

Results—Characteristics independently associated with montelukast treatment failure included age of asthma onset <10 years old (OR = 2.39; 95% CI = 1.17–5.02; $p = .018$), need for steroid burst in the last year (OR = 2.39; 95% CI = 1.13–5.09; $p = .022$), and pre-bronchodilator forced expiratory volume in 1 s (FEV₁) (OR = 1.44 per 10% lower % predicted; 95% CI = 1.07–1.97; $p = .016$). A montelukast failure index was generated from these three variables (range: –5 to 7 points). Scores <0 predicted low risk (<0.20) of treatment failure, whereas scores >5 predicted high risk (>0.60) of treatment failure.

Conclusion—Early asthma onset, worse asthma control in the last year, and lower pre-bronchodilator FEV₁ are associated with montelukast treatment failure. A montelukast failure index is proposed to quantify the risk of failure prior to treatment initiation.

Keywords

asthma; leukotrienes; therapy

Introduction

The clinical course of asthma is characterized by recurrent episodes of wheezing, shortness of breath, and impaired quality of life. Symptom control can frequently be achieved with twice-daily inhaled corticosteroid (ICS) therapy (1–3). ICS therapy may be associated with adverse effects (4–6); therefore, treatment guidelines for asthma management recommend that therapy should be stepped down once adequate control has been achieved (1–3, 7, 8). Physicians are faced with several therapeutic options for step-down therapy including transitioning to lower doses of ICS, once-daily combination ICS/beta-agonist, or oral therapy with leukotriene receptor antagonists such as montelukast (Singulair®, GlaxoSmithKline) (8–12). Montelukast acts via antagonism of the leukotriene receptor resulting in attenuated bronchoconstriction. The leukotriene antagonist montelukast has minimal adverse effects and is available as a once-daily oral formulation, therefore having the potential to increase adherence (13–17).

The “Leukotriene or Corticosteroid or Corticosteroid- Salmeterol Study” (LOCCS) evaluated the efficacy of three different treatment strategies in well-controlled mild asthma (18). LOCCS randomized 500 patients who were controlled on twice-daily low-dose ICS to one of the following treatments: continued twice-daily ICS, once-daily combination ICS/beta-agonist inhaled therapy, or once-daily oral montelukast. Treatment was administered for 16 weeks in a double-masked manner. The LOCCS publication described the frequency of treatment failure with different step-down therapies for mild, controlled asthma. While more patients failed therapy with montelukast (30.0%) than those receiving continued ICS or combination therapy (20.2% and 20.4%, respectively), 70% were successfully treated with montelukast alone.

Characterizing factors associated with montelukast treatment failure may allow clinicians to better determine which patients will not fail step-down to montelukast. The goal of the present analysis was to examine the montelukast-treated LOCCS participants to determine clinical and demographic characteristics associated with treatment failure when stepping down to montelukast. In addition, we developed a montelukast failure index to be used as a

clinical scoring system for physicians to predict the risk of treatment failure when stepping down to montelukast.

Methods

Patient Selection

The 165 patients randomized to montelukast therapy in the original LOCCS study were used to determine associations between enrollment variables and treatment failure. All subjects randomized in LOCCS underwent a 4- to 6-week run-in period, during which open-label fluticasone was administered. Adequate control at 4–6 weeks was defined by all of the following: demonstration of adherence, a pre-bronchodilator forced expiratory volume in 1 s (FEV₁) of at least 80% predicted (19), a score on the Asthma Control Questionnaire (ACQ) of less than 1.5, fewer than 16 puffs of rescue beta-agonist in the final 2 weeks and no hospitalizations, urgent care visits, oral corticosteroid use, or increased ICS use in the run-in period. After the run-in period, eligible participants were randomized to montelukast. Demographic and clinical characteristics for this analysis were obtained from the initial enrollment visit prior to the run-in period. Asthma control measures and lung function measurements at the randomization visit were also obtained. Specific demographic characteristics included age, self-reported race, gender, and self-reported smoking history (never, former, and current). Asthma characteristics included age of asthma onset, need for emergency visits or steroid bursts in the last year, and daily use of specific asthma medications. Asthma severity was characterized using two asthma scores: Asthma Symptom Utility Index (20) (ASUI) and ACQ (21). The ASUI score ranges from 0 to 1, with higher scores indicating fewer symptoms (less severe asthma). The ACQ ranges from 0 to 6, with high scores indicating less well-controlled asthma. Pulmonary function measurements included pre-bronchodilator FEV₁, pre-bronchodilator forced vital capacity, peak flow, and post-bronchodilator FEV₁. All pulmonary function measurements were expressed as percent predicted (19).

As in the LOCCS trial, treatment failure was defined as the occurrence of any of the following during the 16-week study: hospitalization or urgent medical visit for asthma initiated by the patient or physician, use of systemic corticosteroids or need for open-label use of ICSs for asthma as determined by the study physician or asthma care provider, a decrease in pre-bronchodilator FEV₁ to more than 20% below the baseline value measured at randomization, a decrease in the morning peak expiratory flow rate to more than 35% below the baseline value on two consecutive days, use of 10 puffs or more of rescue beta-agonist for two consecutive days (except pre-exercise), refusal by the patient to continue because of lack of satisfaction with treatment, or cessation of therapy due to safety concerns by the study physician. All participants in LOCCS provided informed written consent. The LOCCS study received Institutional Review Board (IRB) approval from each participating institution.

Data Analysis and Generation of Montelukast Failure Index

After stratifying montelukast-assigned participants by occurrence of treatment failure, summary statistics [mean (SD), median (Interquartile range (IQR)), or number (%)] were

computed. Fisher's exact test and the Wilcoxon rank-sum test were used to compare categorical and continuous variables, respectively. A p -value of less than .05 was used to infer statistical significance. Univariate and multivariate logistic regression models were generated to evaluate the associations between individual clinical/demographic variables and treatment failure. Sensitivity and specificity were used to assess the predictive performance of the selected regression models. The chance of treatment failure was expressed as risk (e.g., 0.20), representing the probability of treatment failure over follow-up time.

Using the method described by Sullivan et al. (22), a montelukast failure index was developed. The agreement between the risk estimates based upon the failure index and the regression models was compared using Pearson's correlation, intraclass correlation coefficient (23), and percent agreement for pre-specified risk of treatment failure groups (<10%, 10–20%, and >20%). To assess the generalizability of the montelukast failure index, the index was separately applied to the other treatment groups of the LOCCS trial, consisting of 168 participants continued on twice-daily fluticasone and 162 participants assigned to once-daily fluticasone/salmeterol.

All data were analyzed with R version 2.5.1 (R Developmental Core Team: R Foundation for Statistical Computing, Vienne, Austria, 2007) and Stata software (Stata Corp.: Stata Statistical Software: Release 10.0, Stata Corporation, College Station, TX, USA, 2007).

Results

Baseline Characteristics

Of the 165 participants, 50 (30%) experienced treatment failure during the 16-week follow-up period. Age, gender, smoking history, pre-existing medical conditions, and daily asthma medications were similar between those with montelukast treatment failure compared with those with no treatment failure (Table 1). Individuals experiencing treatment failure were more likely to be non-White and have a younger age of asthma onset (5 vs. 12 years, $p = .01$) compared with those without treatment failure. More participants with treatment failure required steroid bursts in the 12 months preceding enrollment (42% vs. 23%, $p = .01$). Those who failed montelukast treatment had lower baseline FEV₁ compared with those without montelukast failure (81.5% vs. 87.0% predicted, $p = .01$). Prior montelukast use was not significantly associated with treatment failure ($p = .12$).

Multivariate Model Generation and Assessment

After adjusting for potential confounding, age of asthma onset, pre-bronchodilator % predicted FEV₁, and need for steroid bursts in the prior year measured from enrollment were significantly associated with treatment failure (Table 2). Asthma onset prior to the age of 10 was associated with a 2.39-fold increase in the odds of montelukast treatment failure (95% CI = 1.17–5.02; $p = .018$). For every 10% decrement in % predicted FEV₁, the odds of montelukast treatment failure increased by 44% (OR = 1.44 per 10% predicted; 95% CI = 1.07–1.97; $p = .016$). The need for a steroid burst in the past year was associated with a higher odds of treatment failure (OR = 2.39; 95% CI = 1.13–5.09; $p = .022$). When excluding FEV₁ from the multivariate model, the estimates and levels of significance for age

of asthma onset and need for steroid bursts in the prior year were relatively unchanged. When using FEV₁ from randomization rather than baseline visit, the FEV₁ association was no longer significant ($p = .84$).

We calculated the sensitivity and specificity of the model across a range of predicted risks of treatment failure (Figure 1). Determining the optimal threshold for predicting treatment failure requires a trade-off between sensitivity and specificity. This depends in part upon the perceived risk of continuing ICSs versus the perceived risk of experiencing treatment failure after switching to montelukast. Assuming the goal of the model is to balance type I and type II error rates, the optimal threshold of predicted treatment failure is represented by the convergence of the sensitivity and specificity lines in Figure 1. For this model, the optimal cut-point occurs at a predicted risk of treatment failure of 0.309 which yields a sensitivity of 67.3% (95% CI = 52.4–80.1%) and specificity of 67.9% (95% CI = 58.3–76.4%). When setting the model for high sensitivity for treatment failure at 90% and 80%, the associated specificity for treatment failure was 8% and 51%, respectively. The risk of treatment failure at sensitivities of 90% and 80% are 0.1239 and 0.2428, respectively. Conversely, selecting high specificity for treatment failure (90% and 80%), the associated sensitivity for treatment failure was 41% and 49%, respectively. The risk of treatment failure at specificities of 90% and 80% are 0.4446 and 0.3717, respectively.

Montelukast Failure Index: Generation and Performance Characteristics

Using the regression coefficients from the multivariable model, a weighted montelukast failure index was derived (Table 3). This index assigned a range of points for the three clinical variables evaluated in logistic regression modeling. The possible scores range from –5 to 7, with a higher cumulative score associated with a higher risk of montelukast treatment failure. For example, using this index, a patient with age of asthma onset less than 10 years, pre-bronchodilator FEV₁ of 80% predicted, and need for steroid burst in the last year would have a montelukast failure index of 5. Table 4 lists the estimates of risk of montelukast failure across index points. The hypothetical patient described with a montelukast failure index of 5 would be predicted to have a risk of failure of 0.60. An index of less than 0 predicted low risk (<0.20) of treatment failure, whereas a score of greater than 5 predicted high risk (>0.60) of treatment failure. Stratifying the montelukast treatment group by index scores allows for the evaluation of index performance in predicting treatment failure. Of the 161 participants randomized to montelukast with complete follow-up data, 51 had an index score less than 0, 106 ranged between 0.5 and 5, while 4 had an index greater than 5. The treatment failures in these three score strata were 16% (95% CI = 7–29%), 36% (95% CI = 26–56%), and 75% (95% CI = 19–100%), respectively ($p = .0034$).

The fit of the montelukast failure index with the predictive values from logistic regression is represented graphically in Figure 2. As can be seen, across a range of scores, the risk of failure was similar between the montelukast failure index and the logistic regression model. A high degree of agreement was present when quantitatively comparing the agreement between the montelukast failure index and the logistic regression model. The Pearson's correlation was 0.99 (95% CI = 0.98–1.00). The percent agreement comparing the

categorization into risk groups of <10%, 10–20%, and >20% was 93.6% (95% CI = 88.5–97.0%) while the intraclass correlation coefficient was 0.989 (95% CI = 0.985–0.992).

Assessment of Model Discrimination

To determine if the montelukast failure index is specific for predicting montelukast treatment failure, or rather simply identifies patients at higher risk of failure regardless of the type of step-down therapy, we applied the montelukast failure index to the other treatment groups of the LOCCS trial. In LOCCS, a total of 168 participants were continued on twice-daily fluticasone while 162 were assigned to once-daily fluticasone/salmeterol. The occurrence of treatment failure was similar in both groups (20%). The key risk factors for treatment failure identified in the montelukast-treated group (age of asthma onset, need for steroid burst in last year, and % predicted FEV₁) were not associated with treatment failure in either the fluticasone monotherapy or fluticasone/salmeterol groups (see Supplementary Table 1 available online at [http://informahealthcare.com/doi/suppl/\[doinumber\]](http://informahealthcare.com/doi/suppl/[doinumber])). When applied to the fluticasone monotherapy group, the failure index had similar sensitivity but lower specificity than when applied to the montelukast treatment group (see Supplementary Table 2). For the fluticasone/salmeterol group, the montelukast failure index had lower sensitivity and specificity at predicting treatment failure than when applied to the montelukast treatment group.

Discussion

In this analysis, we have identified factors associated with montelukast treatment failure during step-down therapy among individuals with mild intermittent asthma on low-dose ICSs. These factors include younger age of asthma onset, lower FEV₁ % predicted, and need for any steroid burst in the prior year. Using these data, we have computed a montelukast failure index that, after further validation, can be used to predict the probability of treatment failure for patients who are being considered for montelukast therapy as part of a step-down plan for mild asthma controlled on ICSs. A montelukast treatment failure index of less than 0 predicts a low risk of treatment failure, whereas a score of greater than 5 is associated with a high risk of montelukast treatment failure.

The predictors of montelukast treatment failure identified in this analysis (younger age of asthma onset, lower %predicted FEV₁, and need for a steroid burst in the prior 12 months) conform to the clinical picture of an individual with asthma of longer duration and worse recent control. Prior publications have examined predictors of treatment failure during down-titration from ICS. Leuppi et al. (24) found that airway hyperresponsiveness and older age were associated with failure after ICS step-down. Belda et al. (25) identified increase in blood or sputum eosinophils as a predictor of failure after ICS step-down. Similar to our analysis, prior studies have identified longer disease duration, worse pulmonary function, and asthma control as predictors of poor response to montelukast in cohorts with mild-to-moderate persistent asthma (26, 27). Our analysis identifies the mildest group of controlled asthmatics as those with the greatest likelihood of success with montelukast step-down therapy.

What is striking is the magnitude of effect the observed measures have on the odds of treatment failure. Having an early age of onset (<10 years old) is associated with a 2.4-fold increase in the odds of montelukast treatment failure, similar in magnitude to the need for a steroid burst in the prior year. However, each 10% decrement in % predicted FEV₁, a clinical marker frequently used to determine disease severity, confers a smaller increase in the odds of montelukast treatment failure. This index incorporates these different parameters into a simplified system in a manner that weights each covariate appropriately. Such an approach allows physicians to take readily obtainable data and incorporate it into a clinical decision tool. It has been shown that characteristics prior to down-titration may be more informative than baseline characteristics when predicting treatment failure during step-down from ICS (24). The montelukast failure index incorporates patient characteristics obtained prior to a run-in period. We did not observe an association between randomization spirometry measures and treatment failure. This can be explained by the exclusion of those with poor control after the run-in period, thereby potentially eliminating those with the highest risk of treatment failure. This observation highlights that our findings are most applicable to individuals who are able to be well controlled on ICS prior to step-down.

By evaluating the performance of the montelukast failure index in the fluticasone and fluticasone/salmeterol treatment groups of LOCCS, we are able to determine if our index was specific to montelukast or could be applied to other step-down therapies as well. We observed that the montelukast failure index demonstrates similar sensitivity, but not specificity, in determining risk of failure in fluticasone-treated participants. Moreover, the failure index had a low sensitivity and specificity in predicting risk of treatment failure with fluticasone/salmeterol combination therapy. The similar sensitivity observed in predicting treatment failure with montelukast and fluticasone monotherapy suggests that our index may be more applicable in predicting failure of anti-inflammatory step-down treatments. However, these data do not support the use of the failure index in predicting treatment failure with bronchodilator-containing regimens.

The recently updated National Asthma Education and Prevention Program guidelines highlight the need to assess symptom control as well as disease severity (2). The asthma control score is frequently used in clinical trials to assess symptom burden. In our analysis, the inclusion of pre-bronchodilator FEV₁ into the model completely attenuated the associations of the asthma control score with treatment failure. This suggests that in a population of mild asthmatic subjects, measure of airflow obstruction may be as effective as symptom burden in predicting treatment failure. We observed that pre-bronchodilator FEV₁ was more predictive of treatment failure than the post-bronchodilator FEV₁. While it can be difficult to obtain pre-bronchodilator spirometry (because patients must withhold relevant medications), there are increased resources and time required to perform post-bronchodilator spirometry. Thus, post-bronchodilator spirometry has only limited benefit in predicting montelukast treatment failure.

This analysis does have some limitations that warrant discussion. First, the montelukast failure index presented here should be more rigorously validated in an external data set. This is important given the relatively small sample size and the fact that patients included in this analysis were all enrolled in a clinical trial, which may confer some differences to the

general population. The predictive value of the montelukast failure index applies to a population with asthma control defined according to the LOCCS protocol. The definitions of asthma control and asthma stability in the LOCCS protocol differ from some published guidelines which may limit applicability to clinical practice conditions. However, it is reassuring that the factors identified in this analysis agree with clinical logic. The LOCCS trial incorporated a 6-week run-in stability period. Current guidelines recommend 3 months of stability prior to consideration of step-down therapy (1). The estimates of risk of treatment failure predicted by the montelukast failure indices are relevant only to a 16-week time frame, associated with the study duration in LOCCS. Due to the small number of treatment failures, we may have been underpowered to detect other important predictive variables. This could contribute to the observed sensitivity and specificity of the failure index. Further evaluation of this model may offer an assessment of its utility in longer term prediction of montelukast treatment failure.

In summary, this article identifies several factors associated with montelukast treatment failure: younger age of asthma onset, steroid bursts in the last year, and lower FEV₁% predicted. Assessment of these clinical variables is an efficient way to determine both disease control and severity. We have proposed an easily calculated montelukast failure index to predict montelukast treatment failure in individuals with mild asthma controlled on ICSs that are being considered for step-down therapy. Such an index, which incorporates historical and spirometric variables, would allow clinicians to determine the risk of montelukast treatment failure prior to treatment, which makes it ideal for use in developing a step-down therapy plan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of Interest

Dr. Peters serves as an advisor to the DCC of the American Lung Association (ALA) Asthma Clinical Research Centers and served as principal investigator of the ALA Asthma Clinical Research Centers' LOCCS trial which was supported by an unrestricted grant to the ALA by GlaxoSmithKline. Dr. Castro received \$10,001–\$50,000 from Astmatx in consultancy fees; \$5001–\$10,000 from Genentech in advisory board fees; \$50,001–\$100,000 from AstraZeneca, \$10,001–\$50,000 from Boehringer- Ingelheim, \$10,001–\$50,000 from Pfizer, \$5001–\$10,000 from Genentech, and \$10,001–\$50,000 from Merck in lecture fees; more than \$100,001 from Astmatx, more than \$100,001 from Amgen, more than \$100,001 from Centocor, more than \$100,001 from Ception, more than \$100,001 from Genentech, more than \$100,001 from GlaxoSmithKline, more than \$100,001 from MedImmune, more than \$100,001 from Merck, and more than \$100,001 from Novartis in industry-sponsored grants; and \$1001–\$5,000 from Elsevier in royalties. Dr. Irvin has received grant support from the ALA and National Institutes of Health. He has served as a board member for Methapharm and received payment for lectures from Merck. He has received royalties for work related to now up-to-date. Dr. Wise has served as a paid consultant for AstraZeneca, Boehringer-Ingelheim Pharmaceuticals, GlaxoSmithKline, Pfizer, Novartis, Sunovion, Telacris, and Spiration. He has received research grants from Boehringer-Ingelheim Pharmaceuticals and GlaxoSmithKline. Funding for this publication was made possible in part by a Mentored Patient-Oriented Research Career Development Award (K23) from the National Institutes of Health-National Heart, Lung and Blood Institute (MBD). Funding for the original LOCCS study was provided in part by the ALA and GlaxoSmithKline. The authors alone are responsible for the content and writing of the paper.

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Figure 1.

Plot of sensitivity and specificity for logistic regression model. The sensitivity (black line) and specificity (grey line) are plotted across a range of risks of treatment failure predicted by the logistic regression model, with the point of convergence of the two lines representing the optimal probability for maximal accuracy.

Figure 2.

Comparison of the risk of failure predicted by the montelukast failure index and logistic regression model. Across a range of scores, the risk of failure was similar between the montelukast failure index and the logistic regression model.

Table 1

Characteristics of montelukast-only LOCCS participants by treatment failure.

Treatment failure	Yes	No	P-value ^a
<i>N</i>	50	115	
Age (years) [mean(SD)]	31 (17)	33 (15)	.50
Race or ethnic group [<i>N</i> (%)]			
White	25 (50)	79 (69)	.04
Non-White			
Black	17 (34)	24 (21)	
Hispanic	6 (12)	9 (8)	
Other	2 (4)	3 (3)	
Female sex [<i>N</i> (%)]	24 (48)	47 (41)	.40
Smoking history [<i>N</i> (%)]			
Current	2 (4)	3 (2)	.18
Former	12 (24)	17 (15)	
Never	36 (72)	95 (83)	
Asthma characteristics			
Age of asthma onset [median (IQR)]	5 (2–16)	12 (5–24)	.01
Emergency visits in the past 12 months [<i>N</i> (%)]	20 (40)	31 (27)	.10
Steroid bursts in the past 12 months [<i>N</i> (%)]	21 (42)	26 (23)	.01
Daily asthma medications [<i>N</i> (%)]			
Long-acting beta-agonists	3 (6)	6 (5)	>.99
Short-acting beta-agonists	15 (30)	32 (28)	.85
Inhaled corticosteroid	26 (52)	62 (54)	.85
Oral anti-leukotrienes	13 (26)	17 (15)	.12
Asthma scores [mean (SD)]			
ASUI score (range 0–1)	0.9 (0.1)	0.9 (0.1)	.47
Asthma Control Questionnaire (range 0–6)			
Enrollment	1.8 (0.9)	1.5 (1.0)	.11
Randomization	0.6 (0.4)	0.6 (0.4)	.58
Enrollment spirometry [mean (SD)]			
FEV ₁ (% predicted)	81.5 (13.3)	87.0 (12.5)	.01
FVC (% predicted)	94.4 (16.6)	95.4 (11.2)	.50
Peak flow (% predicted)	93.5 (19.1)	92.4 (18.0)	.87
Baseline spirometry [mean (SD)]			
FEV ₁ (% predicted)	91.9 (10.9)	91.7 (11.2)	.84
FVC (% predicted)	100.6 (12.8)	98.8 (12.2)	.40
Peak flow (% predicted)	98.1 (18.4)	94.7 (18.8)	.27
Other conditions [<i>N</i> (%)]			
GERD	15 (30)	31 (27)	.71
Sinusitis	16 (32)	31 (27)	.57
Hay fever/allergic rhinitis	33 (66)	71 (62)	.73

Note: ASUI, Asthma Symptom Utility Index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; LOCCS, Leukotriene or Corticosteroid or Corticosteroid-Salmeterol Study.

^a *P*-values are calculated using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Table 2

Multivariate model of montelukast treatment failure.

	Regression coefficient (SE)	Odds^a or odds ratio (95% CI)	P-value
Intercept	-1.41 (0.30)	0.24 (0.13–0.44)	<.001
Early asthma onset (<10 years old)	0.87 (0.37)	2.39 (1.17–5.02)	.018
FEV ₁ (per 10% decrease in predicted)	0.37 (0.15)	1.44 (1.07–1.97)	.016
Steroid burst in last year	0.87 (0.38)	2.39 (1.13–5.09)	.022

Notes: CI, confidence Interval; FEV₁, forced expiratory volume in 1 s. FEV₁, centered at 80% predicted.

^aIntercept represents odds of an individual with asthma onset 10 years old, FEV₁ 80% predicted, and no steroid bursts in last year. Age, gender, smoking status, urgent care visits in the last year, Asthma Symptom Utility Index (ASUI) and Asthma Control Questionnaire (ACQ) scores, additional spirometric measures, and pharmacotherapies were not significantly associated with increased risk of treatment failure. Odds ratios adjusted for other variables in the model.

Table 3

Montelukast failure index.

Variable	Points
Asthma onset	
10+ years old	0
<10 years old	2.5
FEV ₁ (% predicted)	
55–65	2
66–75	1
76–85	0
86–95	–1
96–105	–2
106–115	–3
>115	–5
Steroid burst in last year	
No	0
Yes	2.5

Note: FEV₁, forced expiratory volume in 1 s.

Table 4

Predictive risk of montelukast treatment failure.

Total points	Estimate of risk ^a
-5.0	0.04
-3.0	0.08
-2.5	0.09
-2.0	0.11
-1.0	0.15
-0.5	0.17
0	0.20
0.5	0.23
1.0	0.26
1.5	0.30
2.0	0.34
2.5	0.38
3.0	0.42
3.5	0.47
4.0	0.51
4.5	0.56
5.0	0.60
6.0	0.69
7.0	0.76

Note:

^a Estimate of risk reflects the predicted risk of treatment failure derived from the montelukast treatment failure score.