



## Letter

## Effectiveness of montelukast in overweight and obese atopic asthmatics

Among the 2 obese-asthma phenotypes (early-onset/atopic and late-onset/nonatopic), patients have increased asthma severity,<sup>1</sup> decreased asthma control,<sup>1,2</sup> and decreased response to inhaled corticosteroids (ICSs),<sup>3–6</sup> the first-line treatment for all patients with persistent asthma. In vitro studies of rat alveolar macrophages have found that leptin enhances cysteinyl leukotriene production.<sup>7</sup> In obese patients with asthma, body mass index (BMI) correlated with leukotriene synthesis,<sup>8</sup> suggesting that leptin perpetuates cysteinyl leukotriene-mediated inflammation in obese patients with asthma. A post hoc analysis of 4 double-blind, placebo-controlled studies noted that with increasing BMI, asthma control decreased in patients using ICSs but remained stable in those using leukotriene antagonists.<sup>3</sup> Because ICSs are not as effective in treating obese patients with asthma, and leukotrienes may be an effective target in obese asthma, there is a need to determine whether montelukast may be more useful in obtaining asthma control among obese patients with asthma. The primary objective of this study was to determine whether montelukast is more effective in obtaining asthma control among overweight or obese patients with early-onset asthma than in normal weight patients with asthma.

We conducted a prospective, randomized, double-blind controlled study in which patients with mild to moderate, persistent, early-onset/atopic asthma received montelukast (5 mg; age, 7–14 years; 10 mg; age,  $\geq 15$  years) or placebo for 24 weeks, in addition to their background ICSs. Patients were characterized as being overweight/obese or normal weight based on Centers for Disease Control and Prevention guidelines. At baseline and weeks 4, 8, 16, and 24 after randomization, the following end points were assessed: Asthma Control Test (ACT) scores, exhaled nitric oxide, spirometry measurements, asthma control, exacerbations, and total ICS dose. ICS doses were stepped down if patients had achieved adequate asthma control, according to the National Heart, Lung, and Blood Institute guidelines. Baseline, midpoint, and final fasting serum and urine studies were obtained to measure leptin, adiponectin, and urinary leukotriene E<sub>4</sub>. Serum and urine samples were stored at  $-80^{\circ}\text{C}$ . After defrosting to room temperature, serum leptin and adiponectin were measured by enzyme immunoassay (SPI Bio, Montigny le Brettonneux, France). After defrosting urine to room temperature, an aliquot was purified using cysteinyl leukotriene affinity sorbent (Cayman Chemical, Ann Arbor, Michigan). Urinary leukotriene E<sub>4</sub> levels were measured by enzyme

immunoassay (Cayman Chemical). The results were normalized to creatinine concentration determined in the sample using by colorimetric assay (Cayman Chemical).

The 2-sample *t* test was used to compare montelukast treatment to placebo at week 12 and week 24 separately. Laboratory parameters were analyzed on the log scale but were back-transformed and reported as geometric means with their corresponding 95% confidence intervals. Two-way analysis of variance was used to test the interaction between treatment (montelukast vs placebo) and weight subgroup (overweight/obese or normal weight). A Bonferroni adjustment for multiple comparisons was performed. A result was considered statistically significant at  $P < .025$  (0.05/2).

A total of 26 patients were enrolled, and 16 completed the study. At the end of the study, there were 4 patients in each of the 4 subgroups: overweight/obese receiving montelukast, overweight/obese receiving placebo, lean receiving montelukast, and lean receiving placebo. No significant differences were found between the groups at the outset of the study with respect to any demographic or clinical variables. The median age in the montelukast group was 10 years (interquartile range, 9.5–14.5 years), and the median age in the placebo group was 9 years (interquartile range, 8–15 years). The montelukast group had 58% males, and the placebo group had 36% males. The 2 treatment arms were comparable in terms of weight (age-specific BMI percentiles, 79.75th vs 76.6th percentile;  $P < .69$  at baseline and 70.3th vs 66.5th percentile,  $P < .94$  at completion of the study). For the 3 adults, we were unable to compare the 2 groups because of the small sample size. There were no significant findings at 12 weeks ( $n = 22$ ). At 24 weeks ( $n = 16$ ), there was a significant difference between montelukast ( $n = 8$ ) and placebo ( $n = 8$ ) for ACT score (24.5 vs 18.1,  $P < .01$ ) and percentage of peak expiratory flow (104.1% vs 83.62%,  $P < .04$ ). There were no significant differences between montelukast and placebo for the remaining spirometry parameters, exhaled nitric oxide, beclomethasone equivalents, or laboratory parameters at week 24. Within overweight/obese and not normal weight patients, there was a significant difference between montelukast and placebo for ACT score (25.0 [ $n = 4$ ] vs 15.7 [ $n = 4$ ],  $P < .01$ ) (Table 1). In addition, at 24 weeks, within normal weight patients ( $n = 8$ ), there was a significant difference between montelukast and placebo for percentage of peak expiratory function (108.1% vs 74.4%,  $P < .02$ ) (Table 1). Overweight/obese patients ( $n = 8$ ) had a significantly higher baseline serum leptin level than normal weight patients (median, 36.0 pg/mL vs 3.1 pg/mL,  $P < .001$ ). There was no difference in the other laboratory parameters assessed. Neither serum nor urine testing results predicted responses to montelukast or correlated with any of the clinical parameters.

Although limited by sample size and poor subject retention, this is the first study, to our knowledge, that assessed treatment

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**Table 1**

Interaction and Subgroup Analyses for ACT Score, Pulmonary Function Parameters, Exhaled Nitric Oxide, or Beclomethasone Equivalents at Week 24

| Variable                     | Overweight/Obese |         |         |         | Normal Weight |         |        |         | Interaction P Value<br>(Treatment × Subgroup) |
|------------------------------|------------------|---------|---------|---------|---------------|---------|--------|---------|-----------------------------------------------|
|                              | Montelukast      | Placebo | MD      | P Value | Montelukast   | Placebo | MD     | P Value |                                               |
| ACT score                    | 25.00            | 15.75   | 9.25    | .01     | 24.00         | 20.50   | 3.50   | .30     | .23                                           |
| FEV <sub>1</sub> , %         | 83.37            | 71.59   | 11.78   | .29     | 97.87         | 85.31   | 12.56  | .26     | .96                                           |
| FVC, %                       | 91.01            | 76.21   | 14.80   | .27     | 101.68        | 88.87   | 12.81  | .34     | .91                                           |
| FEV <sub>1</sub> /FVC ratio  | 83.13            | 80.42   | 2.89    | .63     | 88.25         | 89.35   | −1.10  | .85     | .63                                           |
| FEF <sub>25%–75%</sub> , L/S | 87.62            | 66.99   | 20.63   | .29     | 103.77        | 78.57   | 25.20  | .20     | .86                                           |
| PEF, %                       | 100.19           | 92.79   | 7.39    | .56     | 108.09        | 74.44   | 33.64  | .02     | .16                                           |
| FeNO, ppb                    | 14.33            | 39.50   | −25.17  | .19     | 25.75         | 27.25   | −1.50  | .93     | .36                                           |
| Beclomethasone equivalents   | 680.00           | 1210.0  | −530.00 | .09     | 580.00        | 740.0   | −160.0 | .59     | .38                                           |

Abbreviations: ACT, Asthma Control Test; FEF<sub>25%–75%</sub>, midexpiratory phase; FeNO, fractional exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; MD, mean difference; PEF, peak expiratory flow; ppb, parts per billion.

responses to a leukotriene antagonist in only obese patients with early-onset/atopic asthma. Previous studies investigating the effectiveness of asthma controller medications in obese patients with asthma did not differentiate between the 2 obese-asthma phenotypes. Although this study was limited by its small sample size and poor retention rate, it found that montelukast may be a better controller medication in obese patients with early-onset/atopic asthma than in lean patients with atopic asthma because ACT scores were significantly higher in the overweight/obese group compared with the lean group treated with montelukast. Participant retention was challenging because it was a relatively long study for the mostly pediatric patients. Patients did not want repeated blood draws, and parents wanted to minimize medication regimens. Although ACT is a validated tool in assessing asthma control, it is subjective. Considering the limited sample size, the difference in ACT scores demonstrates the strength of this difference. Because a leukotriene antagonist was more effective in the overweight/obese group, our findings support the idea that leukotriene-mediated inflammation may play a role in perpetuating symptoms in the obese patients with early onset/atopic asthma. Because of the limited effectiveness of ICSs in this patient population, future studies should focus on clarifying the pathophysiologic basis of obese-asthma phenotypes to help discover targeted therapies for this patient population.

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