Montelukast reduces airway eosinophilic inflammation in asthma: a randomized, controlled trial

E. Pizzichini*, J.A. Leff†, T.F. Reiss‡, L. Hendeles§, L-P. Boulet‖, L.X. Wei¶, A.E. Efthimiadis*, J. Zhang*, F.E. Hargreave


ABSTRACT: Leukotrienes are pro-inflammatory mediators which may contribute to tissue, sputum, and blood eosinophilia seen in allergic and inflammatory diseases, including asthma. Montelukast is a cysteinyl leukotriene (CysLT1) receptor antagonist which improves asthma control; the aim of this study was to investigate its effect on induced sputum eosinophils.

Montelukast 10 mg (n=19) or placebo (n=21) were administered orally once in the evening for 4 weeks to 40 chronic adult asthmatic patients, aged 19–64 yrs, in a double-blind, randomized, parallel group study. Patients were included if, at prestudy, they had >5% sputum eosinophils, symptomatic asthma with a forced expiratory volume in one second ≥65% of the predicted value and were being treated only with “as needed” inhaled β2-agonists. In addition to sputum eosinophils, blood eosinophils and clinical endpoints were also assessed.

Four weeks of montelukast treatment decreased sputum eosinophils from 7.5% to 3.9% (3.6% decrease, 95% confidence interval (CI) 1.6–6.0%). In contrast, placebo treatment was associated with an increase in sputum eosinophils from 14.5% to 17.9% (3.4% increase, 95% CI 3.5–9.8%). The least squares mean difference between groups (-11.3%, 95% CI -21.1– -1.4) was significant (p=0.026). Compared with placebo, montelukast significantly reduced blood eosinophils (p=0.009), asthma symptoms (p=0.001) and β2-agonist use (p=0.001) while significantly increasing morning peak expiratory flow (p=0.001). Montelukast was generally well tolerated in this study, with a safety profile similar to the placebo.

These results demonstrate that montelukast decreases airway eosinophilic inflammation in addition to improving clinical parameters. Its efficacy in the treatment of chronic asthma may be due, in part, to the effect on airway inflammation. Eur Respir J 1999; 14: 12–18.

Asthma is associated with increased eosinophils in the airways, lung tissue and peripheral blood, which can correlate with asthma severity [1]. Airway eosinophilia has been observed in chronic stable asthma, after allergen inhalation and during exacerbations [2–5]. When activated by various stimuli, eosinophils cause inflammation by releasing toxic products including oxygen radicals, basic proteins, cytokines and cysteinyl leukotrienes (Cys-LTs) [6]. Bronchial inflammation is considered to be a cause of symptoms and airflow limitation in asthma.

Cys-LTs are chemoattractants for eosinophils in vitro [7]. In guinea-pigs, leukotriene (LTD4) causes eosinophil influx into the bronchoalveolar lavage (BAL), lung tissue, and conjunctiva, all of which are inhibited by (LT) receptor antagonists [8, 9]. In humans, inhalation of LTE4 and LTD4 increase bronchial tissue and sputum eosinophils [10, 11]. Inhibition of LT synthesis decreases airway eosinophils in asthmatic patients [12] and blunts the increase in BAL eosinophils after segmental allergen challenge in allergic patients [13].

Montelukast is a potent, specific, oral cysteinyl leukotriene (CysLT1) receptor antagonist which improves the signs and symptoms of asthma [14–18]. Montelukast treatment also significantly decreases blood eosinophils [15].

Recently, induced sputum has been introduced as a reliable, valid, and responsive method to safely obtain airway secretions [19]. In contrast to BAL and bronchial biopsy, induced sputum has the additional advantage of being noninvasive, thus allowing repeated measurements during treatment [3, 4, 19–23].

In this study, induced sputum eosinophils were measured to investigate the effect of 4 weeks of daily treatment with montelukast on airways inflammation. In this randomized, placebo-controlled, double-blind trial, the effect of treatment on blood eosinophils and clinical outcomes were also evaluated.

Patients and methods

Patients

Symptomatic adult asthma patients capable of producing induced sputum at a prestudy visit, with a proportion of eosinophils >5%, were consecutively enrolled in the study.
(table 1). The diagnosis of asthma was established by symptoms of asthma and by an improvement in the prebronchodilator forced expiratory volume in one second (FEV1) $\geq 15\%$ after salbutamol (200 µg). The asthma was mild as indicated by an FEV1 between 60 and 85% of predicted. All patients had a minimum level of daytime symptoms (weekly score of at least 32 out of a possible 168), and required inhaled $\beta_2$-agonists on an as-needed basis (weekly average, 1 puff·day$^{-1}$) as recorded on a daily diary card completed during the week before allocation. The asthma was stable; there had been no exacerbations or need for any other treatment for one month, and no hospitalizations for asthma occurred within in 3 months of the prestudy visit. Specifically, no patient had previously used an antileukotriene drug. Patients in 3 months of the prestudy visit. Females of childbearing potential had a respiratory tract infection within 3 weeks before the exercise regimen. None had an unresolved sinus or upper (with a smoking history of no more than 10 pack-yrs), were otherwise healthy, were nonsmokers for at least 1 yr had previously used an antileukotriene drug. Patients in 3 months of the prestudy visit. Specifically, no patient needed exacerbations or need for any other treatment for one month.

Clinical measurements

Patients recorded the number of as-needed $\beta_2$-agonist puffs used, morning and evening PEF (the best of three measures using a Mini-Wright peak flow meter (Clement Clark Inc., Columbus, OH, USA)), and daytime asthma symptom scores on a daily diary card validated for its measurement and linguistic properties [24]. Spirometry was performed according to American Thoracic Society criteria [25] between 06:00 h and 09:00 h, ~8–10 h after the previous (bedtime) dose of study drug. For each time point, the best FEV1 value from at least three measurements was used for analysis. Reversibility was determined by administering salbutamol 200 µg through a spacer device (Aerochamber$^\text{TM}$, Monaghan Medical Corporation, Plattsburgh, NY, USA) and measuring FEV1 10–30 min later. Allergy skin tests were carried out by the skin prick technique with a minimum of five aeroallergen extracts appropriate to the geographical location. A weal diameter at least 3 mm larger than the diluent control was considered positive.

Sputum and blood examination

Study site personnel were trained to perform sputum induction and processing in a standardized manner. Sputum was induced as described by PIs et al. [22] with an aerosol of hypertonic saline (3, 4 and 5%) generated by a Fisoneb$^\text{TM}$ ultrasonic nebulizer (Canadian Medical Products Ltd., Markham, Ontario, Canada). Sputum separated from saliva was processed as described by Pizzichini et al. [19]. Briefly, sputum was treated by adding four volumes of 0.1% dithiothreitol (DTT), sutylpsin 10% (Calbiochem Corp., San Diego, CA, USA) followed by four volumes of Dulbecco’s phosphate-buffered saline (D-PBS). The suspension was filtered through a 48-µm nylon gauze (BBBSH Thompson, Scarborough, Ontario, Canada) and total cell counts of leukocytes and cell viability (trypsin blue exclusion method) were determined. The cell suspension was adjusted to 1.0 $\times$ 10$^6$ cells·mL$^{-1}$ and cytotoxic centrifuge preparations were made using 60 µL of the cell suspension (Shandon III cytocentrifuge, Shandon Southern Instruments, Sewickly, PA, USA). Four cytopsins were made, air dried, coded and sent to a central laboratory for reading (St. Joseph’s Hospital, Hamilton, Ontario, Canada). Two were stained by Wright’s stain for a differential cell count on at least 400 nonsquamous cells, and two were fixed in Carnoy’s fixative and stained with toluidine blue for a differential cell count on at least 1,500 metachromatic cells (mast cells and basophils). Squamous cells were measured as a percentage of the total cell population; results of the other cells were expressed as a percentage of the total nonsquamous cell count.

Blood was collected in venoject tubes and sent to a central laboratory (Covance Central Laboratory Services

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Montelukast</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects M/F</td>
<td>12/7</td>
<td>12/9</td>
</tr>
<tr>
<td>Age (range) yrs</td>
<td>31 (19–64)</td>
<td>28 (19–62)</td>
</tr>
<tr>
<td>Atopic n</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Asthma symptom score</td>
<td>2.5±0.83</td>
<td>2.17±0.70</td>
</tr>
<tr>
<td>$\beta_2$-agonist use puffs·day$^{-1}$</td>
<td>4.70±2.9</td>
<td>4.10±2.8</td>
</tr>
<tr>
<td>PEFa.m. L·min$^{-1}$</td>
<td>424±72.2</td>
<td>429±81.8</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>69.2±10.9</td>
<td>68.9±14.7</td>
</tr>
<tr>
<td>Sputum eosinophils %</td>
<td>6.9±9.1</td>
<td>14.1±14.2</td>
</tr>
<tr>
<td>Blood eosinophils $10^5$ cells·mL$^{-1}$</td>
<td>0.36±0.19</td>
<td>0.51±0.29</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. M: male; F: female; PEFa.m.: morning peak expiratory flow; FEV1: forced expiratory volume in one second.
Table 2. – Sputum cell counts

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Treatment</th>
<th>Cells</th>
<th>Difference in least-squares mean*</th>
<th>95% CI of difference %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Last visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophil</td>
<td>Placebo</td>
<td>14.54±14.40</td>
<td>17.90±19.79</td>
<td>-11.27</td>
</tr>
<tr>
<td></td>
<td>Montelukast</td>
<td>7.53±9.52</td>
<td>3.88±4.67</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>Placebo</td>
<td>35.83±19.45</td>
<td>33.12±22.88</td>
<td>7.23</td>
</tr>
<tr>
<td></td>
<td>Montelukast</td>
<td>41.47±28.27</td>
<td>45.85±29.32</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>Placebo</td>
<td>1.80±1.38</td>
<td>1.68±1.19</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Montelukast</td>
<td>1.41±1.54</td>
<td>1.49±1.08</td>
<td></td>
</tr>
<tr>
<td>Macrophage</td>
<td>Placebo</td>
<td>47.19±17.52</td>
<td>46.96±21.50</td>
<td>-1.23</td>
</tr>
<tr>
<td></td>
<td>Montelukast</td>
<td>49.32±26.93</td>
<td>48.33±28.64</td>
<td></td>
</tr>
<tr>
<td>Bronchial epithelial cell</td>
<td>Placebo</td>
<td>0.43±0.86</td>
<td>0.35±0.52</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Montelukast</td>
<td>0.28±0.43</td>
<td>0.46±0.88</td>
<td></td>
</tr>
<tr>
<td>Metachromatic cell</td>
<td>Placebo</td>
<td>0.11±0.12</td>
<td>0.11±0.19</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Montelukast</td>
<td>0.08±0.07</td>
<td>0.08±0.06</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±sd, single value or range. *: analysis of covariance. CI: confidence interval. +: p=0.026.

Inc., Indianapolis, IN, USA), which analysed blood chemistry, haematology and differential (including eosinophil) cell counts.

**Slide reading**

All slides were independently evaluated by two readers blinded to treatment, study site and visit. The average value for each cell type was calculated. A previous validation study using the same readers employed in this study demonstrated that the one week concordance correlation coefficient [26] within reader was >0.98, while between readers was >0.99 [19].

**Statistical analysis**

The percentage change in sputum eosinophils from baseline (the allocation visit) to the Week-4 value (primary hypothesis) was analysed using an analysis of covariance (ANCOVA) model including factors for centre, treatment, and baseline. The ANCOVA model was used to adjust differential regression to the mean effects due to the imbalance in baseline values. While sputum eosinophils had to be >5% at the prestudy visit, some baseline (allocation visit) values were <5%. Therefore, a confirmatory analysis was performed on patients with baseline sputum eosinophils >3% (considered significantly elevated [27]) to exclude baseline values too low to show meaningful decreases during treatment. Treatment by baseline interaction was also evaluated as was the change from baseline to the Week-1 (first visit after allocation) value using the same model. The average treatment period change from baseline for peripheral blood eosinophils was also compared between treatment groups using this model. Post-allocation sputum eosinophil data were excluded from analysis if prespecified criteria confounding efficacy measurements, such as an upper respiratory tract infection occurred within 5 days after randomization (prespecified criteria). All allocated patients were included in clinical endpoint and safety analyses.

**Results**

**Patient allocation and exclusion from sputum analysis**

Forty eligible patients were randomized to active treatment (19 to montelukast, 21 to placebo). Three patients in the montelukast group did not have Week-4 sputum samples available. Two of these patients were discontinued, one owing to an adverse event (abdominal pain) and one owing to a protocol deviation. Data from one placebo patient were excluded from sputum analysis because an upper respiratory tract infection occurred within 5 days after randomization (prespecified criteria). All allocated patients were included in clinical endpoint and safety analyses.

**Effect of montelukast on sputum and blood cell counts**

The characteristics of sputum cells in each group were examined before treatment. Eleven patients in the montelukast group and 17 in the placebo group had sputum eosinophils >3% at baseline visit. Compared with montelukast, the proportion of sputum eosinophils at baseline was higher in the placebo group whether including all subjects (table 2) or analysing only patients with sputum eosinophils >3% (mean eosinophils of 10.6 and 17.1% for montelukast and placebo, respectively).

While there was some variability in response, the effects of treatment on sputum eosinophils in most patients within each group were similar. Four weeks of treatment with montelukast significantly reduced the percentage of sputum eosinophils. In contrast, there was an increase in sputum eosinophils after treatment with placebo (table 2, fig. 1). These effects were evident after the first week (decrease of 2.6% and increase of 2.0% from baseline for montelukast and placebo, respectively, p=0.177) and progressed over the remaining weeks of therapy. The mean (95% CI)
increase in morning PEF 39.0 (16.8–61.2) L.
agonist use -8.1% (-100.4– -35.7), (p
between treatments in FEV1 (p
Adverse experiences
discontinued due to a laboratory adverse experience.
Laboratory adverse experiences were also infrequent and
telukast patient was withdrawn because of abdominal pain.
due to worsening asthma. One montelukast patient was
similar between montelukast and placebo. No patient was
adverse experiences. One placebo patient was withdrawn
frequency in the montelukast and placebo groups were
There were few clinical adverse experiences and their
Montelukast was generally well tolerated in this study.
Compared with placebo, montelukast treatment produc-
ed a significant reduction (mean (95% CI)) in the daytime
asthma symptoms -0.7 (-1.1– -0.3) (p=0.001) and B2-
agonist use -8.1% (-100.4– -35.7), (p<0.001), and an
increase in morning PEF 39.0 (16.8–61.2) L·min⁻¹,
(p=0.001). There was no statistically significant difference
between treatments in FEV1 (p=0.395) (fig. 3). The only
significant correlation between changes in sputum eosino-
phils and changes in clinical endpoints was seen with per-
cent change in sputum eosinophils -3.6%(-16.6– -0.4) and
3.4%(3.5–9.8) in the montelukast and the placebo group,
respectively. Similar changes were observed in the patients
with sputum eosinophils >3%.
Over the four week treatment, montelukast significantly
reduced the number of peripheral blood eosinophils com-
pared with placebo (fig. 2). The mean difference from baseline
was -0.09 (decrease of 25%) and -0.01 (decrease of 2%)
in the montelukast and placebo groups, respectively
(p=0.009).
Effect of montelukast on clinical endpoints

Compared with placebo, montelukast treatment produc-
ed a significant reduction (mean (95% CI)) in the daytime
asthma symptoms -0.7 (-1.1– -0.3) (p=0.001) and B2-
agonist use -8.1% (-100.4– -35.7), (p<0.001), and an
increase in morning PEF 39.0 (16.8–61.2) L·min⁻¹,
(p=0.001). There was no statistically significant difference
between treatments in FEV1 (p=0.395) (fig. 3). The only
significant correlation between changes in sputum eosino-
phils and changes in clinical endpoints was seen with per-
cent change in sputum eosinophils -3.6%(-16.6– -0.4) and
3.4%(3.5–9.8) in the montelukast and the placebo group,
respectively. Similar changes were observed in the patients
with sputum eosinophils >3%.
Over the four week treatment, montelukast significantly
reduced the number of peripheral blood eosinophils com-
pared with placebo (fig. 2). The mean difference from baseline
was -0.09 (decrease of 25%) and -0.01 (decrease of 2%)
in the montelukast and placebo groups, respectively
(p=0.009).

Adverse experiences

Montelukast was generally well tolerated in this study.
There were few clinical adverse experiences and their
frequency in the montelukast and placebo groups were
similar. Three patients were discontinued due to clinical
adverse experiences. One placebo patient was withdrawn
due to worsening asthma. One montelukast patient was
withdrawn due to sarcoidosis believed by the investigator
to have been present at the prestudy visit; another mon-
telukast patient was withdrawn because of abdominal pain.
Laboratory adverse experiences were also infrequent and
similar between montelukast and placebo. No patient was
discontinued due to a laboratory adverse experience.

Discussion

In this randomized trial, daily treatment with montelukast
for 4 weeks reduced sputum and blood eosinophils and
improved clinical asthma control compared with placebo. A
small effect on sputum eosinophils was seen after 1 week and
this was significant after 4 weeks of therapy. These results
raise the possibility that the decreases in sputum eosinophils
might have contributed to the clinical improvement.

This is the first report of the effect of montelukast on
airway eosinophilic inflammation in humans. The decrease
in eosinophils was identified by the repeated examination
of induced sputum, a method which is noninvasive and has
been shown to be successful, reliable and responsive to
change with treatment [28]. The effect of montelukast on
blood eosinophils has also been demonstrated in previous
studies [16, 17].

The results, not confounded by other asthma treatments,
were obtained in patients with chronic asthma and with a
relatively small sample size. Montelukast treatment, de-
spite a lower baseline, decreased sputum eosinophils,
while an increase was observed in the placebo group. The
direction of the changes, despite baseline differences, pro-
vided strong evidence for a treatment effect by working
against changes expected via regression to the mean [29].
In the absence of a treatment effect, the regression to the
mean would cause changes in the opposite direction,
reducing the treatment effect. Future studies might con-
sider stratifying patients by baseline eosinophil percent-
eges, to ensure they are similar in the treatment groups.

Standard, study-wide methodology to ensure sputum
induction and processing consistency was employed; all
technicians were trained centrally. The use of two inde-
pendent and highly trained haematology technicians to read
the cytopspins minimized potential sources of bias. A vali-
dation of these same two slide readers had previously been
shown to be highly repeatable and concordant [19].

An inhibition of eosinophil chemotaxis by montelukast
may explain the results in this study. CysLTs have been
shown to attract eosinophils, and LT antagonists could

Fig. 1. – The effect of: a) montelukast (n=16); and b) placebo (n=20) on
sputum eosinophils at baseline (Pre) and after 4 weeks (Post) of therapy.
Each point is the mean from two blinded readers. Horizontal bars represent
mean values. The percentage of eosinophils (mean±sd) decreased from
7.53±9.52 to 3.88±4.67 in the montelukast group and increased from
14.5±14.40 to 17.90±19.79 in the placebo group (p=0.026).

Fig. 2. – The effect of montelukast (●) and placebo (○) on peripheral
blood eosinophils at baseline (BL) and 2 and 4 weeks after allocation.
Vertical bars represent mean±SEM. Over the 4-week period, montelukast
caused a significant (p=0.009) reduction compared with placebo in
peripheral blood eosinophils.

Effect of montelukast on clinical endpoints

Compared with placebo, montelukast treatment produc-
ed a significant reduction (mean (95% CI)) in the daytime
asthma symptoms -0.7 (-1.1– -0.3) (p=0.001) and B2-
agonist use -8.1% (-100.4– -35.7), (p<0.001), and an
increase in morning PEF 39.0 (16.8–61.2) L·min⁻¹,
(p=0.001). There was no statistically significant difference
between treatments in FEV1 (p=0.395) (fig. 3). The only
significant correlation between changes in sputum eosino-
phils and changes in clinical endpoints was seen with per-
cent change in sputum eosinophils -3.6%(-16.6– -0.4) and
3.4%(3.5–9.8) in the montelukast and the placebo group,
respectively. Similar changes were observed in the patients
with sputum eosinophils >3%.
Over the four week treatment, montelukast significantly
reduced the number of peripheral blood eosinophils com-
pared with placebo (fig. 2). The mean difference from baseline
was -0.09 (decrease of 25%) and -0.01 (decrease of 2%)
in the montelukast and placebo groups, respectively
(p=0.009).
Effect of montelukast on clinical endpoints

Compared with placebo, montelukast treatment produc-
ed a significant reduction (mean (95% CI)) in the daytime
asthma symptoms -0.7 (-1.1– -0.3) (p=0.001) and B2-
agonist use -8.1% (-100.4– -35.7), (p<0.001), and an
increase in morning PEF 39.0 (16.8–61.2) L·min⁻¹,
(p=0.001). There was no statistically significant difference
between treatments in FEV1 (p=0.395) (fig. 3). The only
significant correlation between changes in sputum eosino-
phils and changes in clinical endpoints was seen with per-
cent change in sputum eosinophils -3.6%(-16.6– -0.4) and
3.4%(3.5–9.8) in the montelukast and the placebo group,
respectively. Similar changes were observed in the patients
with sputum eosinophils >3%.
Over the four week treatment, montelukast significantly
reduced the number of peripheral blood eosinophils com-
pared with placebo (fig. 2). The mean difference from baseline
was -0.09 (decrease of 25%) and -0.01 (decrease of 2%)
in the montelukast and placebo groups, respectively
(p=0.009).

Adverse experiences

Montelukast was generally well tolerated in this study.
There were few clinical adverse experiences and their
frequency in the montelukast and placebo groups were
similar. Three patients were discontinued due to clinical
adverse experiences. One placebo patient was withdrawn
due to worsening asthma. One montelukast patient was
withdrawn due to sarcoidosis believed by the investigator
to have been present at the prestudy visit; another mon-
telukast patient was withdrawn because of abdominal pain.
Laboratory adverse experiences were also infrequent and
similar between montelukast and placebo. No patient was
discontinued due to a laboratory adverse experience.
potentially block these effects. For example, Spada et al. [7] showed LTD₄ to be a potent and selective chemoattractant for human eosinophils at physiologically relevant concentrations. Using radiolabelled eosinophils in guinea-pig conjunctiva, Chan et al. [9] showed administration of LTD₄ induced a 2.5-fold increase in conjunctival radioactivity (a measure of eosinophil chemotaxis) in vivo. Utilizing aerosolized LTD₄, Underwood et al. [8] demonstrated inhaled LTs elevated BAL eosinophils in guinea-pig airways; increased eosinophil numbers were confirmed histologically in the bronchial epithelium and subepithelium. Finally, Laitinen et al. [10] showed inhaled LTE₄ increased eosinophils (but not mast cells, lymphocytes, plasma cells or macrophages) in the lamina propria of the airways of patients with asthma.

Corticosteroids and antileukotriene agents have been shown to affect sputum eosinophils in patients with asthma. In a 3-week placebo-controlled study, inhaled beclomethasone (1,000 μg daily) decreased sputum eosinophils by 73%, (45% decrease with placebo treatment, net difference 28%) [30]. Similarly, inhaled beclomethasone (1,000 μg·day⁻¹) reduced sputum eosinophils in a 4-week study comparing beclomethasone with salmeterol [31], and treatment with budesonide (400 μg·day⁻¹ for 7 days) attenuated the increase in eosinophils after antigen challenge [3]. In the present study, the 48% decrease in sputum eosinophils after montelukast treatment (compared with the 23% increase after placebo) is similar in magnitude (net difference of 71%) to the effects seen with corticosteroids in other studies; however, direct within-study comparisons are necessary to confirm this interpretation. An additional, interesting observation in the present trial is the large improvement observed in most clinical endpoints (PEF, β₂-agonist use, symptoms) which, on average, are greater than the effect seen in other montelukast trials [16, 17]. The explanation for this observation is unknown (and may be a chance variation), but may be due to the selection of patients with more substantial airway eosinophilic inflammation. However, the correlation between improvements in sputum eosinophils and clinical endpoints was generally modest; the relationship between changes in clinical endpoints and airways eosinophils is unknown and awaits further clinical trials.

This study was neither designed nor powered to prospectively determine the correlation between sputum markers and clinical outcomes. Therefore, the weak correlations between improvement in sputum eosinophils and clinical outcomes is likely to be an effect of the small range of
airflow limitation, symptoms and β2-agonist use observed in these mildly symptomatic asthmatic patients. However, it has been reported in prednisone-dependent asthmatics [32] that the improvement in clinical parameters after treatment of asthma with prednisone preceded the complete resolution of sputum inflammatory markers. Additionally, during a programmed reduction in prednisone dose, the inflammatory markers in sputum exacerbated before the clinical outcomes. The improvement of clinical parameters before the improvement of airway inflammation was also observed after treatment in nonprednisone-dependent asthmatics with a severe exacerbation of asthma [33]. These observations indicate that changes in clinical parameters may not be completely explained by changes in airway inflammation.

In summary, these results have shown that montelukast, a leukotriene receptor antagonist, reduced sputum and blood eosinophils, and improved clinical endpoints of asthma. The reduction in eosinophilic inflammation may contribute to the beneficial effects of montelukast in chronic asthma.

Acknowledgements. The authors wish to thank the participating study centres including: R. Dockhorn, J.M.T.C.I., Kansas City, MO; B. Williams, J.B.T. Reference Laboratory, Kansas City, MO; D. Hamilos, P. Korenblat, Washington University, St. Louis, MO; J. Karlix, J. Sherman, University of Florida, Gainesville, FL; S. Tarlo, The Toronto Hospital, Respiratory Division, Toronto, Canada; S. Bissounette, D. De Jesus, for expert clinical advice; M.M. Morris, P. Husssack for sputum induction training; S. Weston for slide readings; G. Noonan for manuscript editing; and D. Weinland for excellent study monitoring.

References


