Steroid naive eosinophilic asthma: anti-inflammatory effects of fluticasone and montelukast

L Jayaram, E Pizzichini, C Lemière, S F P Man, A Cartier, F E Hargreave, M M M Pizzichini

Background: Inhaled corticosteroids and leukotriene receptor antagonists reduce airway eosinophilia and have been used as first line anti-inflammatory therapy for mild persistent asthma.

Methods: A multicentre, randomised, placebo controlled, parallel group study was performed to compare the anti-inflammatory effects of fluticasone propionate and montelukast as measured by sputum eosinophils in 50 adults with symptomatic steroid naive asthma and sputum eosinophilia of >3.5%.

Results: Eighteen patients received low dose fluticasone (250 μg/day), 19 received montelukast (10 mg/day), and 13 were given placebo for 8 weeks. Fluticasone treatment resulted in a greater reduction in sputum eosinophils (geometric mean (SD) 11.9 (2.3)% to 1.7 (0.9)% vs placebo 15.4 (2.4)% to 7.8 (4.2)% p = 0.002), and improvement in FEV₁ (mean (SD) 2.6 (0.9) l to 3.0 (0.9) l vs montelukast 2.8 (0.7) l to 2.8 (0.9) l p = 0.02 or placebo 2.4 (0.8) l to 2.4 (0.9) l p = 0.01). Treatment with fluticasone suppressed sputum eosinophilia within a week while montelukast only attenuated it. The effect of montelukast was maximal at 1 week and was maintained over 4 weeks. The effect of fluticasone was maintained over 8 weeks while that of montelukast was not.

Conclusions: Montelukast is not as effective as low dose fluticasone in reducing or maintaining an anti-inflammatory effect in steroid naive eosinophilic asthma.

Ant-inflammatory treatment is critical in the management of asthma because airway inflammation is regarded as the primary cause of asthma symptoms, exacerbations, reversible airflow limitation, airway hyperresponsiveness (AHR), and remodelling. The latter is thought to contribute to the AHR and development of chronic airflow limitation.

Airway inflammation can be easily measured in induced sputum cell counts. Normal values are well documented and the measurements are reliable, valid, and responsive.

Sputum cell counts demonstrate different types of inflammation due to different causes. These are eosinophilic (due to inhaled allergens or chemical sensitisers to which the patient is allergic or sensitised, or to inadequate steroid treatment), neutrophilic (which can be trivial and non-specific or more intense due to viral or bacterial infections), eosinophilic and neutrophilic, or neither. Differentiating these types is important for refining treatment. For example, eosinophilia responds to adequate steroid treatment while current evidence suggests that, if there is no eosinophilia, steroid treatment is ineffective.

Inhaled corticosteroids such as fluticasone propionate are the gold standard anti-eosinophilic inflammatory therapy. They reduce symptoms, airflow limitation, AHR, exacerbations, hospital admissions, and mortality due to asthma. Leukotriene receptor antagonists such as montelukast also have anti-inflammatory properties, reducing or preventing airway eosinophilia in asthma. When compared with placebo they also improve asthma symptoms, airway function, and reduce asthma exacerbations. As a result, leukotriene antagonists have been acknowledged by some guidelines as acceptable first line anti-inflammatory treatment.

However, there is limited direct evidence to support the use of the leukotriene antagonists as first line anti-eosinophilic inflammatory treatment in comparison with an inhaled steroid. Two large randomised controlled trials compared the clinical efficacy of montelukast or zafirlukast with fluticasone propionate. They showed that the benefit from treatment with the leukotriene receptor antagonists was limited compared with low doses of fluticasone. One cross-over study, not placebo controlled, compared the effects of inhaled fluticasone 200 μg/day with montelukast 10 mg/day on inflammatory markers in induced sputum. Fluticasone was shown to decrease sputum eosinophils significantly after 4 weeks. Montelukast also decreased eosinophils after 4 weeks, but not significantly. Although the authors claimed fluticasone treatment to be superior, the difference between the interventions was not significant.

The primary objective of this study was therefore to compare the magnitude of anti-inflammatory effects of montelukast with fluticasone in subjects with asthma and sputum eosinophilia in a four centre, randomised, double blind, placebo controlled trial over 8 weeks. The anti-inflammatory effects were measured by induced sputum eosinophils.

METHODS

Participants
Adults with persistent symptomatic asthma who had only taken a short acting bronchodilator for at least 2 months were recruited from the chest clinics of three Canadian and one Brazilian research centre (table 1). Asthma was diagnosed by standard criteria or by AHR to methacholine with a PC₂₀ of <8 mg/ml if the FEV₁/SVC was >70% (fluticasone n = 4, montelukast n = 1, placebo n = 2). All subjects had induced sputum eosinophilia of >3.5% (normal <2%). None had symptoms of a cold or flu during the month before the start of the study.

The research ethics boards of the participating centres approved the study and each participant gave written informed consent.

Design of study
This was a four centre randomised, double blind, double dummy, parallel group placebo and active controlled trial.
over 8 weeks which was initiated, planned, performed, analysed and reported without influence from industry. The primary outcome was the effect of treatment on sputum eosinophils. Secondary outcomes were improvement in clinical variables (symptoms, bronchodilator use and pre-bronchodilator FEV₁).

There were six visits to the clinic, each at the same time of day ±2 hours. At the initial visit inclusion and exclusion criteria were reviewed, pre and post salbutamol spirometric tests and sputum induction were performed, and peripheral blood was collected for liver function tests. Subjects who met the entry criteria returned on the following day for visit 2 when clinical characteristics were recorded, allergy skin prick tests and, if necessary a methacholine inhalation test was performed by the methods described by Pizzichini et al. Liver function tests (bilirubin, alanine transaminase, aspartate transaminase, gamma glutamyl transaminase, and alkaline phosphatase) were performed by routine laboratory methods.

### Measurements

Questionnaires were used to document subject characteristics. Symptom severity (chest tightness, shortness of breath, wheezing, cough and nocturnal and/or early morning awakening) was graded on a validated 7 point Likert scale. Symptom scores ranged from 5 (very great deal of discomfort or distress) to 35 (no discomfort or distress); see Table 1 for details.

### Statistical analysis

Descriptive statistics were used to summarise the clinical characteristics of the participants. Variables with non-normal distribution (sputum total cell count and eosinophils) were log transformed before analysis. ANOVA with post hoc analysis adjusted for multiple comparisons were used to determine the comparability between groups at baseline. The effects of treatment on the primary and secondary outcomes were compared using a two factor repeated measures ANOVA adjusted for baseline differences. The within subject factor was repeated measures (or time) before and after treatment. The between subject factors were centre and treatment group. Significant variation between groups was identified by the Tukey test and the p value was adjusted for multiple comparisons. All statistical tests were two sided and significance was accepted at the 95% level. The end point was defined as the last value obtained before any added open label fluticasone. The least clinically important difference in sputum eosinophils after intervention was regarded as a 50% reduction and for FEV₁ a change of >12%.

### Results

Randomisation, withdrawals, exacerbations and compliance

Fifty eligible participants were randomised to the treatment groups: 19 to receive montelukast, 18 to receive fluticasone...
and 13 to receive placebo (fig 1). There were no significant differences in clinical or physiological parameters between the treatment groups at baseline (table 1). One patient in the placebo group was excluded from the study early after randomisation because of protocol violation and was not included in the analysis. Of the remaining 49 patients, one in each group was withdrawn before the end of the study: one on montelukast after 2 weeks and one on placebo after 4 weeks were lost to follow up, and one on fluticasone after 2 weeks had a rash, abdominal discomfort and dysuria. All the available results for these patients before withdrawal were analysed. Four patients exacerbated during the study, requiring open label fluticasone: one on placebo, two on montelukast, and one on fluticasone. One subject exacer-

Effects on sputum eosinophilia

The percentage of eosinophils did not differ significantly between the three groups at the pretreatment visit (table 1). After fluticasone treatment an important decrease in sputum eosinophilia was measured as early as 7 days from a geometric mean (SD) of 11.9 (2.3)% to 2.5 (5.1)% (fig 2). After 4 and 8 weeks fluticasone completely suppressed sputum eosinophilia to 1.7 (4.5)% and 1.7 (5.1)% (table 2, fig 2). Treatment with montelukast only attenuated sputum eosinophilia up to 4 weeks. After 7 days, 4 weeks and 8 weeks montelukast reduced sputum eosinophilia from 10.7 (2.3)% to 3.8 (3.8)% after montelukast after 2 weeks had a rash, abdominal discomfort and dysuria. All the available results for these patients before withdrawal were analysed. Four patients exacerbated during the study, requiring open label fluticasone: one on placebo, two on montelukast, and one on fluticasone. One subject exacer-

Effects on clinical variables

The effects of treatment on clinical variables are shown in table 2. Treatment with fluticasone produced a significant increase in pre-bronchodilator FEV₁ by day 7 (fig 3) which was maintained (fig 4). The mean change in FEV₁ on day 7 was 425 ml (95% CI 151.7 to 698.3) after fluticasone, 33 ml (95% CI −108 to 174) after montelukast, and −142 ml (95% CI −355 to 70) after placebo. By 8 weeks the FEV₁ was increased by 475 ml (95% CI 131 to 820) after fluticasone, 156 ml (95% CI −77.7 to 383) after montelukast, and 125 ml (95% CI −64 to 250) after placebo. The difference between the effects of fluticasone and placebo on FEV₁ was 548 ml (95% CI 73 to 842) and between fluticasone and montelukast was 373 ml (95% CI 26 to 720); p = 0.02 and 0.03 for both comparisons.
Fluticasone or montelukast

In this study we have examined repeatedly at different time points the anti-inflammatory effects of fluticasone and montelukast on the airway eosinophilic inflammation of subjects with steroid naive asthma. The results show that treatment with fluticasone suppresses sputum eosinophils and significantly improves FEV₁. These effects of fluticasone were observed by 7 days and were maintained during the 8 weeks of the study. Treatment with montelukast attenuated and had its greatest effect on airway eosinophilia by day 7 which was maintained throughout the study. Montelukast treatment had no effect on FEV₁.

**DISCUSSION**

In this study we have examined repeatedly at different time points the anti-inflammatory effects of fluticasone and montelukast on the airway eosinophilic inflammation of subjects with steroid naive asthma. The results show that treatment with fluticasone suppresses sputum eosinophils and significantly improves FEV₁. These effects of fluticasone were observed by 7 days and were maintained during the 8 weeks of the study. Treatment with montelukast attenuated and had its greatest effect on airway eosinophilia by day 7. However, in contrast to fluticasone, the effect only lasted 4 weeks. In addition, montelukast had no effect on FEV₁. Placebo treatment did not affect sputum eosinophilia or improve FEV₁. These results are relevant to the treatment of asthma with sputum eosinophilia in patients who are not receiving inhaled steroids, but not to similar patients without sputum eosinophilia.

This is the first study to compare repeatedly at several time points the anti-inflammatory effects of a low dose of fluticasone with montelukast in symptomatic steroid naive asthmatics with airway eosinophilia in a placebo controlled study. The results are consistent with other published observations that have shown that leukotriene modifiers, including montelukast, reduce eosinophilic airway inflammation and that inhaled steroids, including fluticasone, suppress it. The failure of fluticasone to completely suppress sputum eosinophilia during the 8 weeks of the study in six of 18 subjects indicates that some patients may require a higher steroid dose. The novel and unexpected finding was a non-sustained anti-inflammatory effect of montelukast at 8 weeks. This is intriguing and questions the use of montelukast as an alternative anti-inflammatory treatment to inhaled steroid in mild persistent asthma, as suggested by one asthma guideline. The inability of montelukast to maintain a clinically important attenuation of airway eosinophilia at 8 weeks of treatment in the present study does not seem to be due to compliance, nor does it seem to be due to a placebo response or to sample size since this was based on the results of an earlier study when montelukast had a sputum eosinophil lowering effect. The explanation is uncertain. The possibilities are that the anti-inflammatory effect is too selective or weak or that the dose

---

**Table 2** Primary and secondary outcomes at baseline and 8 weeks after treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo Day 0</th>
<th>Placebo Day 56</th>
<th>Fluticasone Day 0</th>
<th>Fluticasone Day 56</th>
<th>Montelukast Day 0</th>
<th>Montelukast Day 56</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induced sputum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cell count (×10⁶/g)</td>
<td>2.0 (2.6)</td>
<td>2.5 (2.3)</td>
<td>3.9 (2.1)</td>
<td>4.9 (1.8)</td>
<td>3.1 (2.3)</td>
<td>4.6 (2.3)</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>15.4 (2.4)</td>
<td>7.8 (4.2)</td>
<td>11.9 (2.3)</td>
<td>1.7 (5.1)</td>
<td>10.7 (2.3)</td>
<td>6.9 (3.8)</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>27.4 (20)</td>
<td>28.7 (23)</td>
<td>28.9 (21)</td>
<td>35.3 (28)</td>
<td>24.2 (1.5)</td>
<td>36.0 (27)</td>
</tr>
<tr>
<td><strong>Clinical parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms score</td>
<td>22.5 (4.5)</td>
<td>28.3 (5.1)</td>
<td>23.2 (6.4)</td>
<td>30.5 (4.3)</td>
<td>25.6 (5.5)</td>
<td>28.5 (5.9)</td>
</tr>
<tr>
<td>Sputum eosinophils (%)</td>
<td>2.7 (1.9)</td>
<td>2.1 (1.5)</td>
<td>3.3 (2.6)</td>
<td>0.8 (0.9)</td>
<td>3.3 (3.1)</td>
<td>2.5 (2.7)</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>2.4 (0.8)</td>
<td>2.4 (0.9)</td>
<td>2.6 (0.9)</td>
<td>3.0 (0.9)</td>
<td>2.8 (0.7)</td>
<td>2.8 (0.9)</td>
</tr>
</tbody>
</table>

**Symptoms score** as in table 1. *P values adjusted for baseline values for comparisons between treatment arms: fluticasone v placebo, p = 0.004; fluticasone v montelukast, p = 0.008; montelukast v placebo, p = 0.9.

**Induced sputum data** are expressed as geometric mean (SD) except neutrophils which are expressed as mean (SD). **Clinical parameters data** are expressed as mean (SD).

---

**Side effects**

One subject who was previously well apart from asthma, and who had no alcohol intake and normal baseline serum liver function tests, developed evidence of a drug induced hepatitis after 2 months of treatment with montelukast. The bilirubin and aspartate transaminase, which were previously normal, rose to 30 mmol/l and 62 U/l, respectively, at the final visit and fell to normal levels 3 weeks after the drug was discontinued.
used, although regarded to give maximal effects, is not enough to prevent further increases in airway eosinophilia due to various stimuli.

This study is also the first to show that low dose fluticasone is more effective than montelukast for controlling sputum eosinophilia in steroid naive asthma. The only other study to compare the effects did not select subjects with sputum eosinophilia or include a placebo control.27 It failed to show a difference in the effects of fluticasone and montelukast on sputum eosinophils and failed to show an anti-inflammatory effect of montelukast on eosinophils after 4 weeks of treatment. Possible explanations for the different results in the latter study include the lack of selection of asthmatics with airway eosinophilia so that there was not enough signal to demonstrate an anti-inflammatory effect,28 or the variable washout period of 3–6 weeks between treatment phases of a crossover design.

The design of the present study has several strengths. One of the is the placebo arm which excludes the regression to the mean as the cause of changes in airway inflammation.29 Another strength is the selection of a homogenous population of patients with eosinophilic inflammation to enable a clear signal of anti-inflammatory effects of the drugs to be shown on sputum eosinophils. However, by selecting our patients we decreased the generalisability of the results to patients with symptomatic asthma who have no eosinophilia. The prevalence of symptomatic non-eosinophilic asthma (sputum eosinophils <2%) in a large population of steroid naive asthma is uncertain. It has been reported to occur in approximately 35–40% of the patients presenting in tertiary clinics.30 On the other hand, the lack of selection of homogenous groups of subjects with asthma may help to explain the lack of the steroid effect on clinical trials which has been reported to be as high as 40%.41

While there has been some recent controversy on the role of eosinophils in the pathogenesis of asthma,22 sputum eosinophilia is an important clinical marker of response to steroid treatment42 and the present results support this. The importance of suppressing airway eosinophilia has been further confirmed by two longitudinal studies which compared the monitoring of asthma treatment using sputum eosinophils with symptoms and FEV1,23,24 Both studies showed that the use of sputum cell counts decreased the exacerbation rates by at least 50% without the need for an increase in inhaled steroid treatment.

The present study also showed an improvement in clinical indices of asthma with fluticasone, as indicated by improvement in symptoms, rescue salbutamol, and FEV1. The same was not observed in the group of subjects on montelukast. Although these results differ from previous publications which show that montelukast has bronchodilator45 and bronchoprotective46 properties and, despite the sample size, had not been estimated for this outcome, the present results are in keeping with our previous publication.18 The greater improvement in FEV1 caused by inhaled steroid over antileukotriene receptor antagonists has been seen in other studies.20,21 In one of these, Busse et al47 found that the addition of low dose fluticasone 88 µg twice daily for 24 weeks to albuterol alone in 533 symptomatic patients improved FEV1, morning and evening PEF, symptom free days, and albuterol use more than montelukast. However, montelukast is an active drug and seems to be effective in some patients. The challenge is to identify how to predict which patients will receive treatment benefit.

We conclude that fluticasone treatment is more effective than montelukast in symptomatic steroid naive adults with asthma who have sputum eosinophilia and who would be expected to improve with steroid treatment. This should question the advisability of using montelukast as first line treatment in these patients. However, the effect of montelukast in symptomatic steroid non-eosinophilic asthma was not studied and still requires investigation.

ACKNOWLEDGEMENTS

The authors thank the subjects who participated in the study; A Efthimiadis, S Carruthers, S Weston, M Prodanuk and S Ferreira for performing the sputum cell counts; and P Hussack, S Goodwin, S Chabloz, M Langevin and Julie Cristina Nunes for performing the clinical procedures.

Authors’ affiliations

L Jayaram, F E Hargreve, Airways Research Group, Firestone Institute for Respiratory Health, St Joseph’s Healthcare and McMaster University, Hamilton, Ontario
E Pizzichini, M M M Pizzichini, NUAPVA, Universidade Federal de Santa Catarina, Florianopolis, Brazil
C Lemiére, A Cartier, Hôpital du Sacré-Cœur de Montréal, Montréal, Québec
S F F Man, University of Alberta, Edmonton, Alberta

This study was partially supported by a medical school grant from Glaxo Wellcome Inc; L Jayaram was supported by a Fellowship from Boehringer Ingelheim (Canada) Inc; F E Hargreve is supported by the Father Sean O’Sullivan Research Centre.

REFERENCES

8 Pizzichini MM. Is sputum eosinophilia a good or poor predictor of benefit from inhaled corticosteroid therapy in asthma? Eur Respir J 2002;20:1359–61
13 Dutoit JI, Salome CM, Woolcock AJ. Inhaled corticosteroids reduce the severity of bronchial hyperresponsiveness in asthma but oral theophylline does not. Am Rev Respir Dis 1987; 136:1174–8
15 Hoeltele T, Kluuki T, Societal and health care benefits of early control of bronchial hyperresponsiveness in asthma at an early stage. Thorax 1999;53:1005–6
16 Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long-term prevention of hospitalization for asthma. Thorax 2002;57:880–4
21 Reiss TF, Chervinsky P, Dockhorn RJ, et al. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma. A

www.thoraxjnl.com

EDITORIAL NOTICE

In the May 2003 issue of Thorax we published a paper by Brusasco and colleagues on the subject of health outcomes following treatment with tiotropium.1 This paper reported the results of two 6 month studies that were combined for the purpose of analysis in this paper. One of these studies had been previously published by Donohue et al in Chest and not referenced by Brusasco and colleagues.2 Thorax wishes to bring the overlap between these two papers to the attention of readers.

Steroid naive eosinophilic asthma: anti-inflammatory effects of fluticasone and montelukast

L Jayaram, E Pizzichini, C Lemière, S F P Man, A Cartier, F E Hargreave and M M M Pizzichini

Thorax 2005 60: 100-105
doi: 10.1136/thx.2004.021634