Asthma

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 (5.1)% than montelukast (10.7 (2.3)% to 6.9 (3.8)%; p = 0.04) or 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 than 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.

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, placebo controlled trial of 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.

Inhaled corticosteroids such as fluticasone propionate are the gold standard anti-eosinophilic inflammatory therapy. They reduce symptoms, airflow limitation, airway hyperresponsiveness (AHR), and exacerbations, and are therefore recommended as first line anti-inflammatory therapy for mild persistent asthma.

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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. Subjects were also instructed on how to complete a diary card of symptoms, peak expiratory flow (PEF) for safety, medication use, and adverse events. They were then randomly allocated to receive daily fluticasone 50 μg two puffs in the morning and three puffs in the evening (250 μg/day) and placebo tablet in the evening, montelukast 10 mg in the evening and placebo inhaler, or placebo inhaler and placebo tablet. Subsequent visits were on days 7, 14, 28 and 36 (visits 3, 4, 5 and 6). The procedures at these included symptom questionnaires and adverse events, review of diary cards, spirometry, induced sputum, and a compliance check. Blood for liver function tests was also taken at day 56.

Exacerbations were defined by a worsening of symptoms requiring treatment with four or more extra puffs/day of short acting β₂ agonist from baseline over 48 hours, or by nocturnal or early morning waking two or more times over baseline, or by a fall in pre-bronchodilator FEV₁ of ≥15% from initial spirometry. If an exacerbation occurred, fluticasone 125 μg two puffs twice daily was added to the treatment; if patients continued to exacerbate they were withdrawn from the trial and treated appropriately.

**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.28 Symptom scores ranged from 5 (most severe discomfort) to 35 (asymptomatic). Daily use of short acting β₂ agonist was also recorded. Allergy skin prick tests, spirometric tests, and methacholine inhalation tests were carried out by standardised methods.29-32 Compliance with medications was checked by weighing inhaler canisters and counting tablets. PEF measurements were performed with a mini-Wright peak flow meter on waking and before bed. Sputum induction33 and processing34 for total and differential cell counts were 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.

**Sample size**

Sample size estimation was calculated for the study primary outcome measure—the difference in sputum eosinophil count between fluticasone and montelukast. In a previous study35 comparing beclomethasone (BDP) with placebo in mildly uncontrolled asthma, BDP 1000 μg daily reduced the baseline sputum eosinophil count from a mean (SD) of 22.5(17.9)% to 7.5(6.8)%. Montelukast has been shown to reduce the sputum eosinophil count in mild asthmatics from 7.5% to 3.9% (95% CI −16.6 to 0.4).18 Based on these data, a sample size of 16 in each active arm would have 80% power to detect an absolute difference of 13% in the reduction in the eosinophil count by fluticasone compared with montelukast at an alpha of 0.05 (two tailed) and a beta of 0.2.

**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 exacerbated at day 7 (placebo) and three at day 14; their results were analysed. Four patients exacerbated during the study, and 1 of each group was withdrawn before the end of the study: one included in the analysis. Of the remaining 49 patients, one in the placebo group was excluded from the study early after randomisation because of protocol violation and was not included in the analysis. Differences in clinical or physiological parameters between 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 exacerbated at day 7 (placebo) and three at day 14; their results were analysed up to these visits. They then received open labelled fluticasone and were improved by the added treatment. Compliance was satisfactory (>=96%).

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)% 4.5 (3.5)% and 6.9 (3.8)% (p = 0.9 in comparison with placebo at the end of the study). Placebo treatment did not significantly affect sputum eosinophilia after 7 days, 4 weeks or 8 weeks. The geometric mean difference between the effects of fluticasone and placebo on sputum eosinophilia was −4.0% (95% CI −10.2 to −1.6), p = 0.002 and montelukast was −2.3% (95% CI −5.2 to −1.0), p = 0.04.

We also examined the effects of the study treatments on sputum eosinophilia as a percentage reduction. The median reduction in sputum eosinophilia after fluticasone on day 7 was 72.7% compared with 56.2% and 34.9% after montelukast and placebo. At 8 weeks the eosinophilia, in comparison with baseline, was reduced by 84.1% after fluticasone, 17.5% after montelukast, and 31.4% after placebo.

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 458 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

4 weeks. In addition, montelukast had no effect on FEV1.

ated and had its greatest effect on airway eosinophilia by day 8 weeks of the study. Treatment with montelukast attenuated and fell to normal levels 3 weeks after the drug was discontinued.

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

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 aspartate transaminase, which were previously normal, developed evidence of a drug induced hepatitis 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>Clinical parameter</th>
<th>Placebo</th>
<th>Fluticasone</th>
<th>Montelukast</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induced sputum</strong></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>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>15.4 (2.4)</td>
<td>7.8 (4.2)</td>
<td>11.9 (2.3)</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>27.4 (20)</td>
<td>28.7 (23)</td>
<td>28.9 (21)</td>
</tr>
<tr>
<td><strong>Clinical parameters</strong></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>
</tr>
<tr>
<td>Salbutamol (puffs/day)</td>
<td>2.7 (1.9)</td>
<td>2.1 (1.5)</td>
<td>3.3 (2.6)</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>
</tr>
</tbody>
</table>

* p values adjusted for baseline values for comparisons between treatment arms: fluticasone vs placebo, p = 0.004; fluticasone vs montelukast, p = 0.008; montelukast vs placebo, p = 0.9.

† Pre-bronchodilator values.

‡ p values adjusted for baseline values for comparisons between treatment arms: fluticasone vs placebo, p = 0.02; fluticasone vs montelukast, p = 0.01; montelukast vs placebo, p = 0.9.

Figure 3 Individual plots of percentage sputum eosinophils at day 0 and at the end of the treatment period (day 56) with placebo, fluticasone (FTC) and montelukast (MTK). At the end of the study fluticasone treatment significantly reduced sputum eosinophils while treatment with placebo or montelukast did not.

Figure 4 Effects of treatment with fluticasone (stars), montelukast (closed circles), and placebo (open circles) on pre-bronchodilator FEV1. Fluticasone treatment produced a significant increase in FEV1, as early as day 7 which was maintained throughout the study. Montelukast treatment had no effect on FEV1.
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,44 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 strengths is the placebo arm which excludes the regression to the mean as the cause of change in airway inflammation. 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.19 20 On the other hand, the lack of selection of homogenous groups of subjects with asthma may help to explain the lack of the steroid response in clinical trials which has been reported to be as high as 40%.21 While there has been some recent controversy on the role of eosinophils in the pathogenesis of asthma,22 23 sputum eosinophilia is an important clinical marker of response to steroid treatment24 25 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 FEV1.26 27 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 bronchodilator26 28 and broncho-protective29 properties and, despite the sample size, had not been estimated for this outcome, the present results are in keeping with our previous publication.16 The greater improvement in FEV1 caused by inhaled steroid over antileukotriene receptor antagonists has been seen in other studies.30 31 In one of these, Busse et al32 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.

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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.

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