



Treatment with inhaled steroids in patients with symptoms suggestive of asthma but with normal lung function

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ABSTRACT: A total of 144 patients with lower airway symptoms suggestive of asthma, but who did not fulfil the functional criteria of asthma, were included in a randomised, double-blind, placebo-controlled 8-week “proof-of-concept” study with mometasone furoate (MF), 400 µg once daily. The primary efficacy variable was the mean change from baseline in six morning and evening weekly symptom scores: cough, sputum production, wheeze, shortness of breath, chest tightness and exercise-induced cough/wheeze. Total symptom scores were calculated after treatment for 4 and 8 weeks.

Compared with placebo, MF improved total morning symptom score at 8 weeks. Changes in total evening symptom scores did not differ between treatments. MF improved all individual symptom scores more than placebo, although the differences in changes between treatments were not always statistically significant. Morning and evening peak expiratory flow rates increased with MF compared with placebo. MF reduced eosinophils and the levels of eosinophilic cationic protein in induced sputum.

The results show that symptoms suggestive of asthma exist in patients without significant β_2 -agonist reversibility or diurnal variability in peak flow. Once-daily MF may benefit some of these patients and a short course with inhaled corticosteroids may be tried. Responders should be better identified in further studies.

KEYWORDS: Airway inflammation, asthma symptoms, induced sputum, mometasone furoate, placebo

Asthma is an inflammatory airway disease characterised by the accumulation of eosinophils, mast cells and T-helper lymphocytes in the airway mucosa and underlying tissues [1, 2]. Patient complaints include episodic or prolonged cough, wheeze, shortness of breath and chest tightness during and after exercise and/or at rest. The diagnosis is based on the demonstration of reversible or variable airway obstruction often associated with increased bronchial hyperresponsiveness (BHR), but does not include the characteristic airway inflammation [3, 4]. However, there are patients with symptoms suggestive of asthma who do not fulfil the asthma lung function criteria, *i.e.* a $\geq 12\%$ increase in forced expiratory volume in one second (FEV₁) 15 min after inhalation of a rapid-acting β_2 -agonist or a $\geq 20\%$ diurnal variability in peak expiratory flow rates [5]. In recent years, inflammatory markers, such as the numbers of eosinophils in induced sputum, concentrations of eosinophilic cationic protein (ECP) in sputum and serum [6, 7]

as well as the levels of nitric oxide in exhaled air [8], have been increasingly used to detect and monitor airway inflammation.

In the general population, the prevalence and incidence of subjects with symptoms suggestive of asthma is higher than those of patients with verified disease [9, 10]. The Finnish Asthma Programme estimated that 5% of the general population suffer from diagnosed asthma [10] but, in addition, up to 10% have episodic symptoms suggestive of asthma but do not fulfil the asthma lung function criteria. For this condition, some authors have used the terms pre-asthma or asthma-like inflammation [11, 12]; it is, however, unknown how many of these patients go on to develop asthma in the future. Often, these patients have recurrent cough as their main symptom. An eosinophilic airway inflammation is a common finding [5, 13–15], although most patients are left without a confirmed diagnosis and the delay in diagnosing asthma may be considerable [16].

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A small survey in Finland showed a mean delay from the initial symptoms suggestive of asthma to a physician-made diagnosis of 19 months in children and 64 months in adults [11, 16]. During the delay, the patients often receive courses of less-effective drugs like antibiotics and antitussives, which do not affect the underlying eosinophilic inflammation.

In a small pilot-type study, treatment with inhaled beclomethasone dipropionate for 3 months significantly reduced symptoms in patients in whom asthma was suspected, but lung function measurements did not confirm the diagnosis [13]. The present study evaluated whether these previous results could be repeated in a larger setting when patients were recruited on a multicentre basis. Whether early anti-inflammatory treatment would benefit this kind of patient or even prevent the development of clinical asthma has not been studied.

The efficacy and safety of mometasone furoate (MF) 400 µg (delivered dose, *i.e.* the dose leaving the inhaler, corresponding to a metered dose of 440 µg in the inhaler) inhaled once daily in the evening was evaluated compared with placebo in patients with symptoms suggestive of asthma but with lung function within the normal range. MF is a glucocorticosteroid, which is delivered *via* a reservoir-type inspiratory-flow driven dry powder inhaler Twisthaler™ (Schering-Plough Corporation, Kenilworth, NJ, USA).

METHOD

Study design

This was a double-blind, placebo-controlled, multicentre study performed at 23 study centres in Finland, Sweden, Norway, Greece, Hungary, UK and Canada. The 1–2 week screening period was followed by 8 weeks of randomised treatment. There were six visits in the study. At visit one, informed consent was obtained, at visit two, subjects were screened and started a 1–2 week run-in period before day one; visit three was a baseline/randomisation visit and thereafter patients attended three clinic visits: after 2, 4 and 8 weeks of treatment.

The primary efficacy variable was the mean change from baseline in weekly morning and evening symptom severity scores. The symptoms, recorded on a 0–3 point scale, were cough, sputum production, chest tightness, shortness of breath, wheeze and exercise-induced cough/wheeze. Secondary efficacy variables were use of reliever medication, changes in eosinophil numbers and ECP in induced sputum, and changes in airway reactivity measured with histamine or methacholine.

Safety was evaluated by recording the number and frequency of treatment-related adverse events.

The present study was conducted in accordance with good clinical practice and with the World Medical Association Declaration of Helsinki. The study protocol and the statement of informed consent were approved by the institutional review boards of each study centre.

Patients

Subjects aged 12–65 yrs were eligible for the study. The main inclusion criteria were: 1) FEV₁ ≥80% predicted 2) cough (with or without sputum production) plus at least one additional symptom from chest tightness, wheezing, shortness of breath, or exercise-induced cough or wheezing for ≥2 months, but

<2 yrs; and 3) average symptom score of ≥1 (scale 0–3) for cough and for sputum production during 7 days of the run-in period. The main exclusion criteria were: 1) physician-diagnosed asthma; 2) a ≥12% increase in absolute FEV₁ during reversibility testing at screening; 3) average daily morning/evening peak expiratory flow (PEF) variability ≥20% for the week prior to baseline; 4) history of smoking within 12 months prior to screening or a smoking history >10 pack-yrs; 5) evidence of chronic obstructive pulmonary disease, chronic cough due to post-nasal drip, asthma, chronic bronchitis, sinusitis or gastro-oesophageal reflux; and 6) an upper respiratory tract infection within 4 weeks prior to screening. In order to exclude chronic cough due to other causes, a careful medical history and radiographs of the chest and paranasal sinuses were obtained. If symptoms of allergic/nonallergic rhinitis were present, the patients were treated accordingly, *i.e.* with nasal corticosteroids and/or antihistamines before the study; such treatment could not be changed during the study.

Treatments, randomisation and blinding

At visit three, patients were randomised to receive treatment with MF, one dose of 400 µg (one puff) in the evening *via* Twisthaler™ (Schering-Plough Corporation), or placebo from an identical-looking inhaler. A salbutamol inhaler could be used as reliever medication. No other medications for respiratory disorders were allowed during the study. Randomisation was performed in a 1:1 ratio according to a computer-generated global randomisation code. The blinded randomisation code was maintained in a sealed envelope.

Assessments

Lower airway symptoms

Every morning and evening, starting at visit two, the subjects evaluated symptoms and signs, and recorded the ratings on diary cards. The symptoms were: wheezing, cough, sputum production, chest tightness, shortness of breath and exercise-induced cough/wheeze. The severity was graded on a scale of 0–3 (0: no symptoms present; 1: symptoms present but not disturbing and not limiting daily activities; 2: symptoms definitely present, disturbing at some time and may limit daily activities; and 3: very marked symptoms, very disturbing most of the time and prevented some daily activities).

For the 7 days prior to the baseline visit, an average combined symptom score for cough and sputum production ≥1 was required for enrolment. The average score was calculated by adding morning symptom scores to evening symptom scores and dividing by 14.

Spirometry and reversibility testing

Spirometry was performed to measure forced vital capacity and FEV₁. The best effort, *i.e.* the highest FEV₁, was recorded. FEV₁ had to be ≥80% pred. A reversibility test was performed at visit two. For this test, subjects received 200 µg of inhaled salbutamol and spirometry was performed 15–20 min later. Reversibility was defined as an increase in absolute FEV₁ of ≥12%; subjects who demonstrated reversibility were excluded from the study.

PEF rates

Subjects measured their PEF every morning and evening throughout the study using a Vitalograph peak flow meter (Vitalograph Ltd, Maids Moreton, England). The highest value of three attempts was recorded. The diurnal variation was calculated using a standard formula:

$$\text{Diurnal variation} = 100\% \times 2 \times (\text{ePEF} - \text{mPEF}) / (\text{ePEF} + \text{mPEF}) \quad (1)$$

where ePEF and mPEF are PEF values measured in the evening and morning, respectively.

Use of rescue medication

Starting at visit two, subjects recorded the number of puffs of salbutamol taken in each 12-h period.

Induced sputum

At visits three and six, induced sputum was collected after subjects were pretreated with 200 µg of inhaled salbutamol. The procedure was carried out in a standardised way as described previously [7]. Subjects were asked to cough during and after inhalation of 5 mL of 3% NaCl solution using an ultrasonic nebuliser for 15 min. The number of eosinophils were counted and the concentration of ECP was measured. An eosinophil score of 0–1 was considered normal and scores of 2–4 abnormal.

Tests of bronchial reactivity

At selected centres, BHR was measured at visits three and six using histamine [17] or methacholine [18]. Provocative concentration causing a 15% fall in FEV₁ (PC₁₅) histamine and provocative concentration causing a 20% fall in FEV₁ (PC₂₀) methacholine were calculated.

Calculation of sample size

A total sample size of ~216 was needed to provide 80% power to detect a treatment difference of 0.5 units for change from baseline for a single symptom when the SD was assumed to be 1.3 and testing was two-sided at the $\alpha=0.05$ level of significance.

Statistical analyses

All statistical analyses were performed on pooled data. No adjustments for covariates or multiple tests were done in the efficacy analyses due to the proof-of-concept type of the study.

The absolute and per cent change from baseline in individual morning and evening symptom scores were summarised by week and treatment, and analysed with an ANOVA model containing the fixed effect of treatment. The 95% confidence interval for the difference between treatments (MF minus placebo) was calculated. Normality assumption of ANOVA was tested using the Shapiro–Wilk test. Treatment differences at baseline were examined using an ANOVA model containing fixed effect of treatment. Analysis based on additive total morning and evening symptom scores was also performed.

The weekly averages of six morning and evening individual symptom severity scores, PEF, and daily salbutamol use were summarised and analysed with the aforementioned ANOVA model. The frequency distribution and the mean and SD were presented. The treatment effect on the rating was analysed with the Mantel–Haenszel test (mean scores).

Frequency distribution of eosinophil scores (0–4 semiquantitative scale) at baseline and end of study were presented by treatment. Chi-squared tests compared treatment groups for proportions of subjects with abnormal findings (score 2–4) at baseline and end of study. For eosinophil scores and ECP, analyses of changes from baseline to end of study were performed with the Mann–Whitney U-test for between treatment group comparison and the Wilcoxon signed rank test for within treatment group comparison. PC₁₅ and PC₂₀ values from airway hyperreactivity testing were summarised by visit.

The incidence (number and percentage) of treatment-emergent adverse events was presented for each preferred term.

RESULTS

Disposition of patients

The disposition of the patients is shown in figure 1. The baseline characteristics of the intention-to-treat population are shown in table 1. They did not differ between patients randomised to treatment with MF or placebo.

The distribution of the six daily symptom scores (morning + evening scores) at baseline on the 0 to 6 scale is shown in table 2.

Compliance

Compliance was calculated as the number of doses taken (recorded in diary cards) divided by the number of doses to be taken and multiplied by 100. The mean compliance was 94% in the MF group and 91% in the placebo group.

Symptom scores

Average morning and evening total symptom scores and cough and wheeze scores by treatment at baseline, and the changes in scores after treatment for 4 and 8 weeks are shown in table 3.

The changes in mean total symptom scores at 4 and 8 weeks are illustrated in figure 2. The total morning symptom score decreased more in MF-treated subjects than in placebo-treated subjects after both 4 and 8 weeks of treatment. After 8 weeks' treatment the difference was statistically significant. The decrease in morning wheeze scores was significantly associated

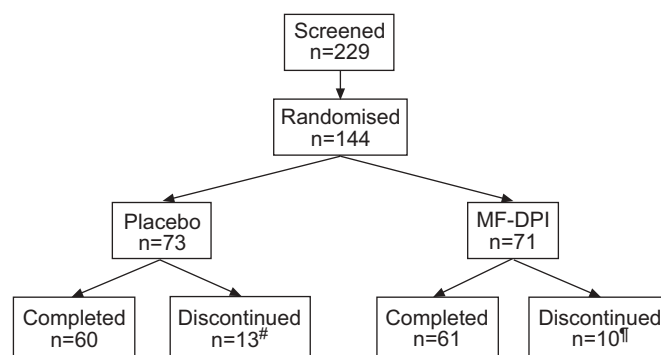


FIGURE 1. Patient flow. Disposition of subjects. MF: mometasone furoate; DPI: dry powder inhaler. #: upper respiratory tract infection (n=1), noncompliance (n=4), did not meet protocol eligibility (n=8); ¶: upper respiratory tract infection (n=1), lymphoma not otherwise specified (n=1), treatment failure (n=2), did not meet protocol eligibility (n=6).

TABLE 1 Patient characteristics at baseline (visit three) in the two treatment groups (intention-to-treat population)

Characteristics	Placebo	MF
Subjects	70	70
Female	52 (74)	47 (67)
Age at entry yrs		
Mean	47 ± 11	45 ± 12
Range	20–64	21–67
Race		
Caucasian	66 (94)	66 (94)
Other	4 (6)	4 (6)
FEV₁ L		
Mean	3.19 ± 0.81	3.13 ± 0.78
Range	1.68–5.41	1.84–5.30
FEV₁ % pred		
Mean	104.2 ± 15.5	103.5 ± 13.2
Range	81–147	75–133 [#]
Reversibility of FEV₁ %		
Mean	3.6 ± 2.8	4.4 ± 3.8
Range	0.0–10.0	0.0–22.0 [†]
Mean ± SEM morning PEF L·min⁻¹	461 ± 13	436 ± 13
Mean ± SEM evening PEF L·min⁻¹	468 ± 13	444 ± 13
PEF variability	5.4 ± 3.2	5.5 ± 3.8
Salbutamol puffs·day⁻¹	0.44 ± 0.86	0.94 ± 0.14
BHR[‡]	14/34	21/36
Atopy[§]	65/70	69/70
Rhinitis		
History of allergic rhinitis	12	18
Actual use of nasal steroids	13	20
Sputum eosinophils		
Score 0–1 (<5%)	46	41
Score 2–4 (≥5%)	8	11
Sputum ECP µg·L⁻¹	714 ± 1343	962 ± 1654

Data are presented as n, n (%) or mean ± SD, unless otherwise stated. MF: mometasone furoate; FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow; BHR: bronchial hyperresponsiveness; ECP: eosinophilic cationic protein. [#]: one patient had an FEV₁ <80% predicted at baseline (visit three). At visit two (the screening visit) all patients fulfilled the inclusion criterion of a FEV₁ >80% pred; [†]: one patient showed a reversibility of FEV₁ of >12% at baseline (visit three). At visit two (the screening visit) all patients fulfilled the inclusion criterion of a reversibility of <12%. [‡]: number of hyperresponsive/number of tested subjects; [§]: number of skin-prick test positive/number of tested patients.

with MF treatment at both time points and decrease in evening wheeze score at 8 weeks.

At the end of the study, about one out of every four patients was free of symptoms, as defined by a symptom score of 0–2 out of 36. There were 18 (26%) such responders in the placebo group and 20 (29%) in the MF group.

Two *post hoc* analyses were performed comparing the changes from baseline in weekly average total symptom scores in patients treated with MF. The first analysis compared the subgroup of patients with sputum eosinophilia at baseline to

TABLE 2 Percentage distribution at baseline of the six daily (morning + evening) symptom scores (scale 0–6) used in the study

Symptom	Symptom scores						
	0	1	2	3	4	5	6
Cough	0.7	3.6	61.2	17.3	13.7	3.6	0
Sputum	30.4	23.9	26.1	9.4	10.1	0	0
Chest tightness	50.4	18.5	17.8	8.9	3.7	0.7	0
Dyspnoea	53.7	21.6	17.9	4.5	0.7	1.5	0
Wheeze	75.2	15.0	4.5	3.8	0.8	0.8	0
Exercise-induced cough/wheeze	47.8	21.6	19.4	4.5	4.5	2.2	0

those without. The second *post hoc* analysis compared patients with or without BHR at baseline. Statistically significant differences between the MF-treated groups were not seen at any time point during the study in either analysis.

Changes in weekly average symptom scores in patients with or without a history of rhinitis (and with or without actual use of nasal corticosteroids) were also analysed. No differences in efficacy were observed between these subgroups of patients. Differences in response between atopic and nonatopic patients were not analysed, as almost all patients were atopic.

PEF

The morning and evening PEF values slightly but steadily increased from baseline in the MF-treated subjects; this did not occur in the placebo group. The increase of morning PEF was significantly more in the MF group from week 4 to week 8, as was the per cent change at each week (weeks 1–8). The change of evening PEF also was also more favourable in the MF group (weeks 5–8), as was the per cent change (weeks 4–8). Figure 3 shows the mean changes in morning and evening PEF values after treatment for 4 and 8 weeks. The differences in change of PEF between MF and placebo were significant for morning PEF at both time points and for evening PEF after treatment for 8 weeks.

Number of doses of salbutamol

The decrease of weekly number of puffs of salbutamol used by the patients in the MF group was significantly larger than by patients in the placebo group at each week (weeks 3–8). The same was true in the per cent change of weekly use of salbutamol at weeks 6 and 7. The proportion of subjects in the MF group who did not use any puffs of salbutamol increased from 47% at baseline to 68% at week 8. The proportion of subjects who used 1–4 puffs of salbutamol weekly, and subjects who took more than four puffs of salbutamol weekly decreased from baseline (18 and 35%, respectively) to week 8 (7 and 25%, respectively).

Eosinophils and ECP in induced sputum

At baseline, 18% of the patients had an abnormally high eosinophil score: 15% in the placebo group and 21% in the MF

TABLE 3 Average morning and evening total symptom scores and cough and wheeze scores by treatment at baseline and the changes in scores after treatment for 4 and 8 weeks

	Morning			Evening		
	Placebo	MF	p-value	Placebo	MF	p-value
Subjects n	70	70		70	70	
Total symptom score						
Baseline [#]	4.32 ± 0.32	4.36 ± 0.32	0.93	4.62 ± 0.32	5.01 ± 0.32	0.39
Week 4	-0.80 ± 0.28	-1.53 ± 0.27	0.06	-1.10 ± 0.27	-1.69 ± 0.27	0.13
Week 8	-1.35 ± 0.28	-2.16 ± 0.27	0.04	-1.65 ± 0.32	-2.25 ± 0.31	0.18
Wheeze score						
Baseline	0.30 ± 0.06	0.33 ± 0.06	0.73	0.30 ± 0.07	0.36 ± 0.06	0.52
Week 4	-0.01 ± 0.04	-0.14 ± 0.04	0.017	-0.02 ± 0.06	-0.16 ± 0.06	0.068
Week 8	-0.04 ± 0.06	-0.21 ± 0.05	0.026	-0.08 ± 0.06	-0.26 ± 0.06	0.040
Cough score						
Baseline	1.35 ± 0.06	1.33 ± 0.06	0.80	1.44 ± 0.06	1.52 ± 0.06	0.37
Week 4	-0.26 ± 0.08	-0.44 ± 0.08	0.12	-0.32 ± 0.07	-0.48 ± 0.07	0.13
Week 8	-0.53 ± 0.10	-0.58 ± 0.09	0.70	-0.56 ± 0.10	-0.58 ± 0.09	0.85

Data are presented as mean ± SEM least-squares, unless otherwise stated. [#]: baseline is the average of days -6 to 1 for morning score and days -7 to -1 for evening score. MF: mometasone furoate.

group. The proportion of MF-treated subjects in whom sputum eosinophils disappeared increased from 79% at baseline to 93% at the end of the study ($p < 0.001$), while no change occurred in the placebo group (85% at both observation points). The mean decrease of ECP from baseline in the MF treatment group was $91 \mu\text{g}\cdot\text{L}^{-1}$, while in the placebo treatment group change increased by $125 \mu\text{g}\cdot\text{L}^{-1}$. This difference was statistically significant ($p = 0.002$). Within the MF subjects, the ECP decreased significantly between baseline and the end of the study (from median 274 to $195 \mu\text{g}\cdot\text{L}^{-1}$; $p = 0.006$).

Safety

Both treatments were well tolerated. The number of subjects with any adverse events did not differ between the groups (45 for MF and 43 for placebo; $p = 0.726$). Most adverse events were mild or moderate. Five severe adverse events were reported in the MF group (dizziness, unspecified ear disorder, throat irritation, sinusitis, musculo-skeletal pain) and six in the placebo group (influenza-like symptoms, toothache, coughing, sinusitis, aggravated coughing and dyspnoea).

There were 18 (25%) subjects with adverse events in the MF group that were possibly associated with treatment, with headache as the most frequently reported adverse event, and 11 (16%) in the placebo group, with dry mouth as the most frequent event. The difference was not significant ($p = 0.149$). Two patients in the MF group discontinued the study due to a diagnosed lymphoma and an upper respiratory tract infection, and one in the placebo group due to a respiratory infection.

DISCUSSION

Asthma patients may have lower airways symptoms for variable periods of time before a functional diagnosis of asthma is made. In patients subsequently diagnosed as asthmatics this prodromal stage can be called pre-asthma. A Finnish survey has demonstrated that delays in seeking help (patients' delay) and

in making diagnosis (doctors' delay) were considerable [11]. However, not all subjects with symptoms suggestive of asthma are asthmatic or will develop the disease [10, 19]. The problem is that symptomatic subjects who may share the same pathophysiology with real asthmatics suffer without adequate treatment because the condition may remain unrecognised for long periods. Thus, it is important to monitor patients with symptoms suggestive of asthma but with lung function still within the normal range.

Cough, as an initial symptom of asthma, is a well-recognised sign of the disease. More than 30 yrs ago GLAUSER [20] described a group of asthmatic women with prolonged cough. These subjects improved with oral corticosteroid therapy and the term "cough variant asthma" was coined. A careful medical history in subjects with cough may disclose wheeze and sometimes a significant reversibility of FEV₁ with bronchodilators [21]. Attention has also been paid to subjects with chronic cough and without asthma, having an eosinophilic bronchial inflammation [14, 15, 22, 23]. Interestingly, patients with chronic cough who are responsive to corticosteroids have been found to resemble patients with asthma in relation to gene expression of some cytokines found in cells from bronchoalveolar fluid [24] and in relation to various inflammatory mediator concentrations [25].

Symptoms other than cough have been associated with early asthma. Therefore, in the present study, subjects were included who had had, in addition to cough, at least one additional symptom of wheeze, chest tightness, shortness of breath, sputum production, or cough and/or wheeze during exercise, but who did not exhibit the functional criteria for asthma. A further sign that the included patients did not suffer from overt clinical asthma was the fact that 75% of the subjects did not report wheeze at all, a symptom most typical of established asthma. Furthermore, patients who had neither

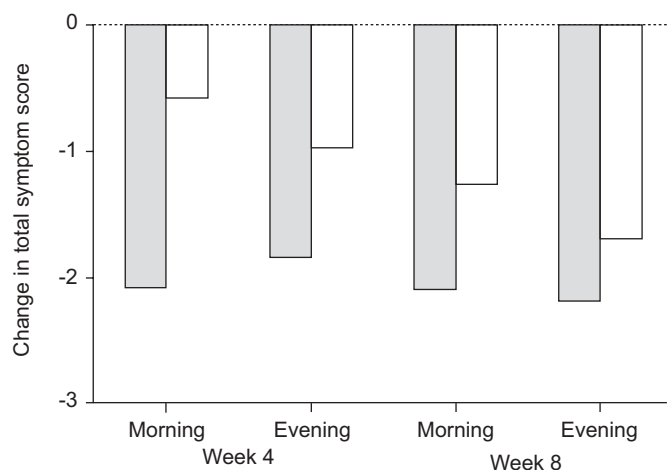


FIGURE 2. Changes in morning and evening total average symptom scores during 8 weeks' treatment with inhaled mometasone, 400 µg in the evening (■), or placebo (□). The p-values for the differences in change were 0.06 and 0.04 at 4 and 8 weeks for morning symptoms, and 0.13 and 0.18 for evening symptoms, respectively.: change=0.

≥12% reversibility of FEV₁ in a bronchodilator test nor PEF variability >20% were included. In fact, the mean FEV₁ reversibility was 4% for the whole study population and the mean PEF variability was only 5.5 L·min⁻¹. Treatment with MF 400 µg once daily in the evening significantly improved all morning and evening symptom scores at some time point compared with placebo.

A significant difference in symptom scores between the MF- and placebo-treated groups was not always seen, probably because of the high variability of symptoms with asymptomatic periods. One limitation of the present study was the relatively small number of patients. It was estimated that a total of 216 subjects needed to be included to demonstrate statistically significant differences in changes of symptom scores compared with placebo. However, only 140 subjects could be recruited within a reasonable period of time. This is surprising, as there are more subjects with symptoms suggesting asthma than patients with diagnosed asthma [6, 7]. The recruitment problems may reflect the fact that subjects with cough and other symptoms but without marked breathlessness attend primary care physicians. Only patients with more-severe symptoms are referred to specialists, who were the investigators in the present study. Nevertheless, treatment with MF compared with placebo decreased symptoms, improved airway function and reduced the percentage of sputum eosinophils. Inevitably, the study population was heterogeneous and included subjects with symptoms not responsive to treatment with an inhaled corticosteroid. This may explain some inconsistencies in the results: MF was better than placebo at some time points but not in all patients and not for all symptoms.

In the present study population, in parallel with symptom reductions, there was a significant improvement in the morning and evening mean PEF values compared with placebo. During the 8-week study, the morning mean PEF value improved by 27 L·min⁻¹ (7%) while no change (2.2 L·min⁻¹; 0.6%) was seen in the placebo group. This demonstrates that treatment with an

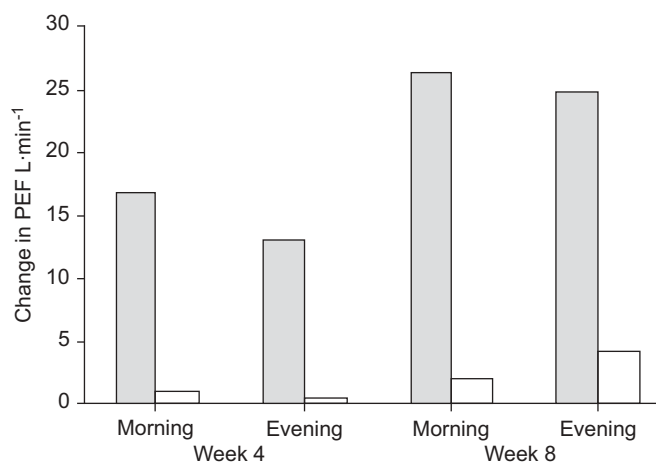


FIGURE 3. Changes in morning and evening peak expiratory flow (PEF) values during 8 weeks' treatment with inhaled mometasone, 400 µg in the evening (■), or placebo (□). The p-values for the differences in change at 4 and 8 weeks were 0.020 and 0.003 for morning PEF, and 0.067 and 0.016 for evening PEF values, respectively.

inhaled corticosteroid benefited the patients, even if they did not show a reversible airway obstruction at baseline or a marked PEF variability during the run-in period (mild hidden obstruction). The efficacy appears to be comparable to that shown in a 3-month study with beclomethasone dipropionate in a similar but smaller study population [13].

Patients with mild persistent asthma usually show eosinophilic airway inflammation at some point in the disease process [1, 2]. The present study found approximately one-fifth of patients to have an increase in sputum eosinophils at baseline. The rate would probably be much higher if repeated measurements of sputum parameters had been performed. When compared with placebo treatment, MF resulted in a reduction in sputum eosinophils and in sputum ECP concentrations. However, despite the observed effect on eosinophils, the presence of sputum eosinophilia at baseline was not predictive of improvement after treatment, as there was no difference in clinical improvement between the patients with and without baseline eosinophilia.

The effect of MF treatment on BHR was difficult to evaluate due to the relatively short intervention and the small numbers of patients tested. Nevertheless, the reduction in symptom scores was not limited to patients with demonstrated BHR.

It is generally agreed that patients with mild persistent asthma should have an inhaled corticosteroid as their first-line treatment, rather than a bronchodilator [26]. In the present study, neither eosinophil counts in sputum nor BHR tests were used as inclusion criteria, and the study population can be characterised as a "real-life" study setting. Clinical studies applying more specific inclusion criteria could give further information about the usefulness of treatment with inhaled corticosteroids. It would be clinically important to know how to detect those who would benefit. Studies performed by the present group, among others, have demonstrated the value of treatment with inhaled corticosteroids in patients with newly detected asthma [27, 28]. After

initial recovery of symptoms and lung function some of them may need only periodic treatment [29], although this has been debated [30, 31]. In addition, patients with mild intermittent asthma exhibit signs of airway inflammation [2, 32] and they also benefit from adding an inhaled corticosteroid to their as-needed therapy with a bronchodilator [32]. Based on the change in symptom scores in the placebo group, it is obvious that not all patients with symptoms suggestive of asthma need treatment with a course of inhaled corticosteroids. The present results do not support initiation of long-term treatment with inhaled corticosteroids in this group of symptomatic patients. However, treatment for a period of weeks or months may be indicated, but any further therapy should be based on results of a thorough follow-up. Further and longer term studies are warranted in order to define the subgroup of patients with symptoms suggestive of asthma, but not fulfilling the functional asthma criteria, and who may benefit from periodical treatment with inhaled corticosteroids.

In a Finnish study of children aged 7–12 yrs, who had lower airway symptoms but normal airway function, it was found that one-third developed asthma during a 2-yr follow-up [19]. Among adults with unexplained cough, 29 (16%) patients out of 182 developed asthma during a 4-yr follow-up period [33]. Such patients may benefit from treatment with an inhaled corticosteroid, but long-term follow-up would be needed.

In summary, patients with symptoms suggestive of asthma but not fulfilling functional asthma criteria represent a heterogeneous group. Far from all of these patients will develop asthma in the future. The present study demonstrates that within the time frame of 8 weeks the symptoms may disappear, both spontaneously and with treatment with mometasone furoate. At a group level, mometasone furoate was significantly better than placebo in reducing symptoms, sputum eosinophils and eosinophilic cationic protein, and improving airway function. However, with the number of patients studied it was not possible to define a subgroup that responds better to treatment. The current authors conclude that a short course with inhaled corticosteroids may be indicated for these patients but that long-term treatment should not be introduced unless a firm diagnosis of asthma is established.

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