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Benefits of low-dose inhaled fluticasone on airway response and inflammation in mild asthma

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KEYWORDS
Mild asthma;
Airway hyperresponsiveness;
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Methacholine inhalation test;
Induced sputum

Summary
Rationale: Current guidelines suggest that asthma should be controlled with the lowest dose of maintenance medication required.
Objectives: To evaluate the effects of a low dose of inhaled corticosteroid compared to a placebo, on airway inflammation and responsiveness in patients with mild symptomatic asthma.
Methods: In this randomized double-blind, placebo-controlled, parallel group study, we looked at the influence of inhaled fluticasone propionate 250 μg/day for 3 months followed by 100 μg/day for 9 months on airway inflammation and methacholine responsiveness in non-smoking subjects with mild allergic asthma. Subjects were evaluated at baseline and 3, 6, 9 and 12 months after treatments; a 2-week evaluation of respiratory symptoms and peak expiratory flow measurements was done before each visit.
Results: Fifty-seven subjects completed the 3-month study period. Airway responsiveness, expressed as the PC_{20} methacholine, increased by 0.27 and 1.14 doubling concentrations,

Abbreviations: AHR, airway hyperresponsiveness; ATS, American Thoracic Society; ECRHS, European Community Respiratory Health Survey; ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in one second; FEV_1/FVC, ratio of forced expiratory volume in one second/forced vital capacity; FP, fluticasone propionate; P, placebo; PC_{20}, provocative concentration inducing a 20% fall in FEV_1; PEF, peak expiratory flows; AM, morning; PM, evening.

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respectively, in placebo-treated ($n = 33$) and in fluticasone-treated ($n = 24$) asthmatic subjects ($p = 0.03$). An additional improvement in PC_{20} up to 2.16 doubling concentrations was observed in the fluticasone-treated group during the 9-month lower-dose treatment ($p = 0.0004$, end of low-dose period compared with placebo). Sputum eosinophil counts decreased after 3 months of fluticasone 250 μg/day compared with placebo ($p < 0.0001$) and remained in the normal range during the 9-month lower-dose treatment. Respiratory symptoms and peak expiratory flows did not change significantly throughout the study in both groups.

Conclusion: In mild asthma, keeping a regular minimal dose of ICS after asthma control has been achieved, may lead to a further reduction in airway responsiveness and keep sputum eosinophil count within the normal range.

Introduction

Inhaled corticosteroids (ICS) are widely used to treat asthma.[1] In mild asthma, fluticasone, at a dose of 1000 μg/day, reduced methacholine responsiveness by slightly less than 2 doubling concentrations over a period of 2 months and significantly reduced airway inflammation.[2] In mild to moderate asthma, low ICS doses also have significant effects on these parameters; a 14-week treatment with fluticasone propionate, 200 μg/day, reduced methacholine responsiveness by 1.86 doubling doses and eliminated the eosinophilic airway inflammation assessed by induced sputum analysis.[3] Previous studies suggested that subjects with mild asthma who are at high risk of asthma exacerbations could particularly benefit from early ICS treatment.[4–11] ICS provided better asthma control than bronchodilators alone in patients with mild asthma not considered to need maintenance treatment.[2,4,12] Ideally, the minimum dose of ICS necessary to maintain asthma control should be used to minimize side effects.[5,7,8,13–17]

Based on the fact that mild asthma is often undertreated and that regular ICS help eliminate airway inflammation and possibly prevent the progression of asthma, the OPTIMA and the START studies evaluated low-dose ICS in mild persistent asthma and showed a reduction of asthma exacerbations after, respectively, one year of treatment with BUD 200 μg/day and 3 years with budesonide 400 μg/day.[4,6,12,18–21] In another study by *Boushey et al.*, a regular one-year treatment with budesonide 400 μg/day had a similar effect on asthma control, frequency of exacerbations and quality of life as an intermittent treatment[22] although the methodology of this study was criticized.[8]

The use of continuous low-dose ICS in mild or mild intermittent asthma was recently evaluated in two studies comparing the effects of fluticasone propionate (FP) at a daily dose of 250 μg, respectively during 11 and 6 months, and resulted in an improvement lung function and airway hyperresponsiveness (AHR) and a reduction of asthma exacerbations.[23,24] However, in one of these studies, 34% of patients were already using ICS before randomisation.[23] In another study, a dose of FP 100 μg twice daily and a daily dose of combined salmeterol 50 μg and FP 100 μg improved similarly peak expiratory flows in ICS-naïve patients with mild asthma albeit FP 100 μg twice daily was better in reducing exacerbations rates.[25]

As few studies analyzed the effect of a prolonged treatment with a low dose of ICS on airway responsiveness (AHR) and inflammation in mild asthma, the objective of this study was to evaluate in patients with clinically controlled mild steroid-naïve asthma previously treated with a short-acting β_2-agonist only whether a low dose of inhaled corticosteroids (100 μg/day during 9 months), which is the lowest dose of the GINA low-dose category, would maintain the improvement in airway inflammation and airway responsiveness obtained after a short-course of low-dose inhaled corticosteroids (3-month course of FP 250 μg/day) in subjects with mild asthma.[26]

Methods

Study design: multicentric double-blind placebo-controlled randomized study comparing fluticasone propionate (FP) 250 μg/day followed by a 9-month maintenance treatment of FP 100 μg/day to placebo in mild steroid-naïve asthmatic subjects.

Subjects

Subjects aged 18–45 years were recruited from Asthma and Respiratory Allergy clinics of participating institutions and from advertisements in local media.

Inclusion criteria included: mild stable asthma with intermittent asthma symptoms (less than twice a week in the last 3 months); a provocative concentration of methacholine inducing a 20% fall in forced expiratory volume in one second (PC_{20} FEV_1) between 0.5 and 16 mg/mL, a $FEV_1 > 70\%$ predicted, current exposure to a relevant indoor allergen, no respiratory infection within 6 weeks of the beginning of the study and use of a short-acting β_2-agonist alone (less than 3 times per week). Patients with a PC_{20} between 8 and 16 mg/mL had a known history of asthma with previously measured $PC_{20} < 8$ mg/mL. All patients were enrolled out of the pollen season to minimize seasonal allergic exposure at entry in the study.

Exclusion criteria included lifetime previous use of any bronchial anti-inflammatory agents; uncontrolled asthma, smoking history >10 packs-years, smoking in the last twelve months and pregnancy, breastfeeding or inadequate contraception.

Study protocol

On baseline evaluation (visits 1—2), subjects completed the ECRHS respiratory questionnaire[27] and had an allergy skin-prick test. A methacholine inhalation test and induced sputum analysis were done twice at a two-week interval. Means of both evaluations were considered as baseline values. Subjects were then randomly assigned by a collaborator not implicated in the study to receive either the placebo during one year or a 3-month course of fluticasone propionate (FP) 250 μg/day followed by a 9-month maintenance treatment of FP 100 μg/day. A subject number was provided to preserve the blinding during the study so that neither the subjects nor the investigators were aware of the treatment group assignment. Treatments were taken blindly with a metered-dose inhaler at 18 ± 2 h. Compliance to therapy was monitored by questionnaire and by checking Diskus counters. Subjects came to the laboratory every 3 months during treatment (visits 3—6) for a methacholine inhalation test and induced sputum analysis. They were questioned on asthma exacerbations (periods of increased asthma symptoms with an increased use or need to use asthma medication) in the period preceding study visits. During the study, they received no corticosteroid treatment except the study medication. Rescue bronchodilators (short-acting β_2-agonist) could be taken on demand. No other asthma medication was allowed.

Symptoms scores and peak expiratory flow (PEF) were measured during 2 weeks at baseline evaluation and every three months during treatment periods.

The primary outcome variable was methacholine airway responsiveness. Secondary outcome variables were airway inflammation measured by induced sputum, respiratory symptoms, peak expiratory flows and asthma exacerbations.

The study was approved by the institutional Ethics Committee and all subjects gave written informed consent.

Study tests

Atopy was confirmed by skin-prick tests with 16 common allergens including household animals, pollens; house dust and house dust mites, moulds and cockroach. Spirometry was done according to current ATS standards using 3 reproducible measurements of FEV_1. Methacholine challenges were done at the same time of day, in the morning, according to a standard method described by *Hargreave et al.*[28] using a calibrated spirometer satisfying ATS recommendations.[29,30] At first visit, the rating of the perception of bronchoconstriction-induced symptoms was determined on a modified Borg Scale (0—10) during the methacholine inhalation test before each FEV_1 measurement.[30,31] Sputum was induced with hypertonic saline by the method described by *Pin et al.*[32] and modified by *Pizzichini et al.*[33]

Symptoms of cough, shortness of breath, chest tightness, wheeze and phlegm production were evaluated daily during 2 weeks before each visit on a scale from 0 to 5, where 0 = no symptoms, 1 = minimal, 2 = light, 3 = moderate, 4 = severe, and 5 = very severe symptoms. Patients noted all scores on a diary card and the mean daily symptoms score was obtained. Peak expiratory flows were measured morning and evening in triplicate, using a mini-Wright device (Allen & Hanburys, Glaxo, Toronto, Montreal) and the best result was kept.

Statistical analysis

Results are expressed as mean ± SD or as otherwise specified.

No formal power calculation was performed. According to a study by Inman *et al.*,[34] we anticipated that a number of 12 subjects per group should be sufficient to observe significant changes in airway responsiveness with 90% power. Regarding airway inflammation, Bettiol *et al.*[35] showed that a sample size of 11 subjects per group had a 70% power to detect a 50% reduction in sputum eosinophil counts.

From subjects' characteristics data, one-way ANOVA and Fisher's exact test were used to analyze continuous and categorical variables respectively. All cell count variables as well as PC_{20} were log-transformed to stabilize variance. Variables expressed in percentage were analyzed using the $\sin^{-1}(\sqrt{})$ transformation.[36] Statistical results from these parameters were expressed with transformed values. To compare groups at baseline and at 3 months, a three-way ANOVA was used to analyze data. One factor (fixed) was associated to the comparison among the groups of subjects (placebo or FP). One factor was linked to the subjects' effect (random nested effect). The third factor (fixed) was associated to the comparison between visits (at baseline and 3 months). This factor was analyzed as repeated measurements. An interaction effect between the fixed factors was added to the statistical model. A compound symmetric structure (with a constant variance and constant covariance) was used as covariance matrix. The same statistical approach was used to compare groups over the time course (3, 6, 9 and 12 months) using a homogeneous first-order autoregressive structure for repeated measurements and using their associated baseline value as covariate. All variables were analyzed using the appropriate transformation (log and $\sin^{-1}(\sqrt{})$ transformations). Statistical results from these parameters were expressed with transformed values. Results of representative measures between 3 and 12 months were expressed using the back transformation with the 95% confidence intervals from least-square means adjusted for baseline values. The univariate normality assumption was verified with the Shapiro—Wilk test and the Brown and Forsythe's variation of Levene's test statistic was used to verify the homogeneity of variances. Multivariate normality was verified with Mardia tests. All assumptions were fulfilled. The results were considered significant with p-values <0.05. The data were analyzed using the statistical package program SAS v9.1.3 (SAS Institute Inc., Cary, NC).

Results

Sixty-nine subjects were enrolled into the study; 34 were randomized in the placebo group and 35 in the treatment group. One subject was excluded in the placebo group because of an exacerbation of asthma which required

treatment with inhaled corticosteroids; there were no other asthma exacerbations throughout the study. The study patient flow is summarized in Fig. 1.

Baseline measures of PC_{20}, FEV_1, FVC and induced sputum parameters

On entry in the study, AHR to methacholine ranged from 0.83 to 16 mg/mL (mean: 4.1 mg/mL) and mean baseline FEV_1 was $99.2 \pm 12.4\%$ of predicted values for all subjects. Subjects' baseline characteristics for the placebo- and FP-treated groups are summarized in Table 1. Mean baseline % predicted FEV_1 ($p = 0.82$), FVC ($p = 0.16$) and PC_{20} were similar in both groups. Mean baseline ratios for FEV_1/FVC were respectively, $82.3 \pm 7.4\%$ and $84.2 \pm 6.2\%$ in the placebo- and the FP-treated groups ($p < 0.0001$). Borg scores (mean $\pm$ SD) at PC_{20} for perception of methacholine-induced respiratory symptoms were not significantly different in subjects from the placebo or FP groups for breathlessness (2.0 ± 1.7 and 1.9 ± 1.2, respectively), chest tightness (1.9 ± 1.0 and 2.4 ± 1.8), wheeze (0.7 ± 1.0 and1.1 ± 1.4), phlegm production (0.9 ± 1.2 and 0.5 ± 0.8) or cough (1.2 ± 1.1 and 1.0 ± 1.0) ($p > 0.05$).

At baseline, means of induced sputum total number of cells $\times 10^6$ of the placebo (0.295, 95% confidence interval (CI): 0.184–0.470) and FP groups (0.382, 0.228–0.637) were similar ($p = 0.12$). Cell differentials were not significantly different between groups for macrophages: (respectively 69, 95% CI: 61–76 and 65, 55–73) $p = 0.24$, eosinophils: (1.3, 0.2–3.2 and 1.7, 1.0–2.5) $p = 0.62$, neutrophils: (26, 17–34 and 28, 20–38) $p = 0.57$, lymphocytes: (1.5, 0.6–2.7 and 0.9, 0.2–2.0) $p = 0.44$ and bronchial cells: (1.4, 0.7–2.4 and 1.9, 0.9–3.2) $p = 0.92$.

Baseline measures of symptoms and PEF

Asthma symptoms measured during the weeks before treatments were similar in the placebo and FP groups with respective average scores of 0.4 ± 0.6 and 0.3 ± 0.5 per day ($p > 0.05$) corresponding to minimal symptoms. Mean AM/PM PEF were respectively $412 \pm 82/423 \pm 84$ L/min in the placebo group and $484 \pm 73/489 \pm 73$ L/min in the FP group,

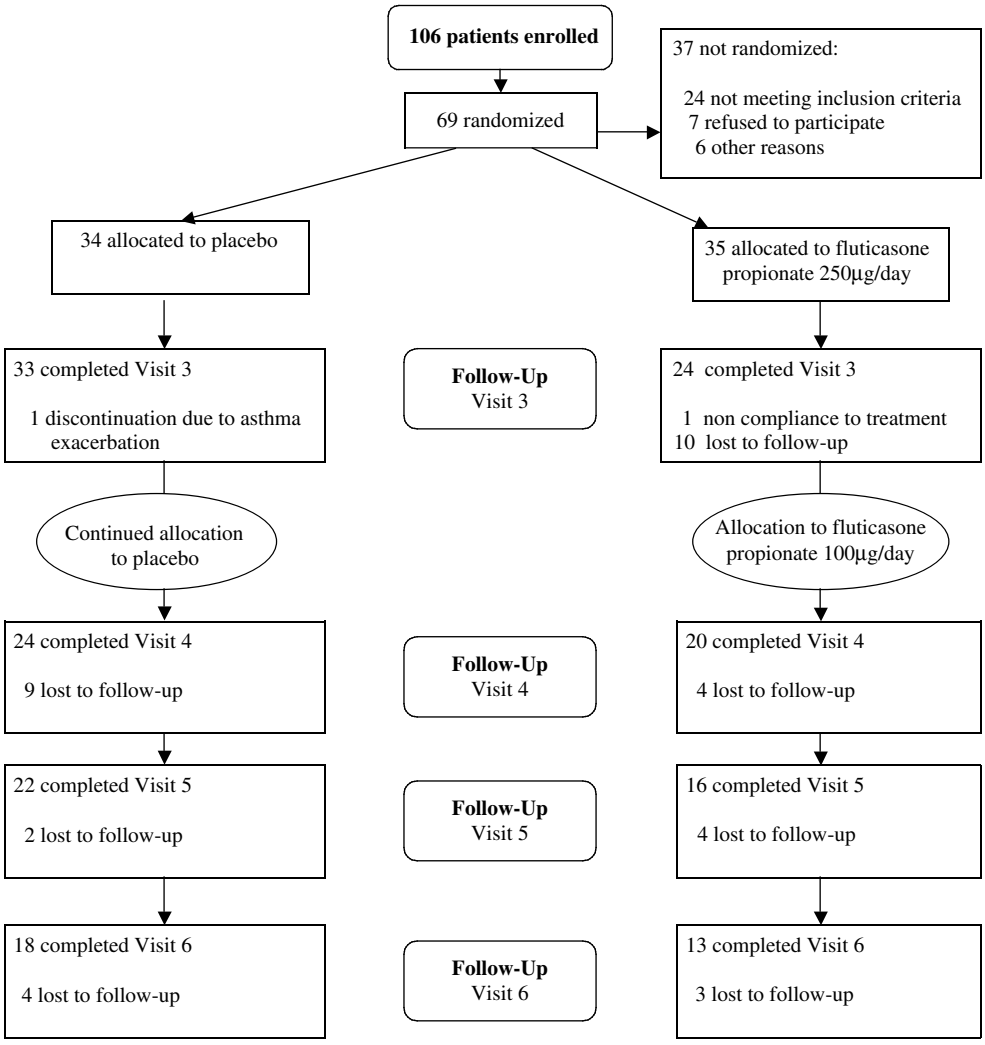

Figure 1 Study patient flow.

Table 1 Subjects' characteristics.

	Mild asthma	
	Placebo group($n = 33$)	FP[a] group ($n = 24$)
Gender M/F	10M/23F	11M/13F
Age (years) Mean ± SD	27 ± 7	26 ± 8
Atopy (n)		
Indoor allergens	33	24
Outdoor allergens	28	19
Smoking status (n)		
Non-smoker	28	18
Ex-smoker[b]	5	6
FEV_1 (L) Mean ± SD	3.33 ± 0.62	3.55 ± 0.62
% predicted	98.5 ± 12.5	97.2 ± 10.5
FVC (L) Mean ± SD	4.09 ± 0.83	4.17 ± 0.77
% predicted	101.6 ± 12.3	97.1 ± 11.6
Ratio FEV_1/FVC ± SD (%)	82.3 ± 7.4	84.2 ± 6.2
PC_{20} (mg/mL) (Geometric mean of baseline visits)	3.2	3.9

[a] FP: Fluticasone propionate.
[b] Ex-smoker: Smoking history <10 pack-years and no smoking in the last year.

corresponding to 81%/82% and 88%/92% of predicted values ($p = 0.006$ between groups).

Expiratory flows and methacholine responsiveness during treatments

During treatment and maintenance periods, FEV_1 increased progressively up to a 6% improvement from baseline at the end of the study in the FP group while it fluctuated in the group placebo and increased only by 1% (Fig. 2, $p = 0.054$ between both groups). Baseline forced vital capacity did not change significantly in any group before and after the treatment period (data not shown). FEV_1/FVC ratios did not vary significantly compared to baseline (both groups: $p > 0.05$) during and after treatment (Table 2).

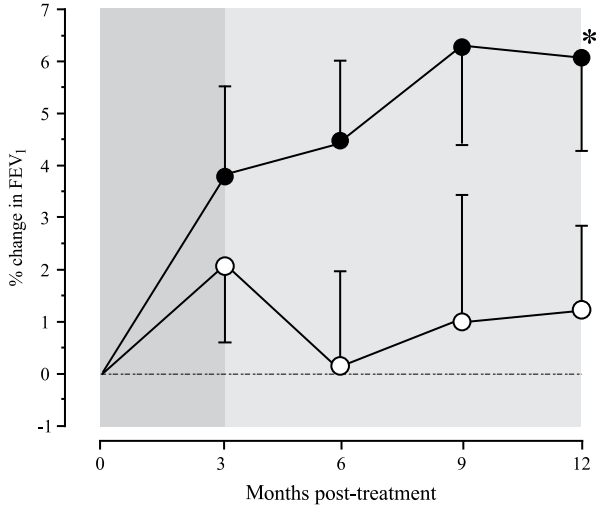

Figure 2 Percent change in FEV_1 before and after treatment (dark shade background) and maintenance treatment (light shade background) for subjects who received placebo (blank circle) or FP (dark circle). Bars represent sem. Compared with baseline FEV_1 at the end of maintenance treatment improved by 6% in the FP group and 1% in the placebo group. *$p = 0.054$.

In the placebo group, AHR did not change from baseline to the 3-month visit with respective mean PC_{20} values of 3.2 and 4.2 mg/mL (Table 2). Mean PC_{20} decreased slightly at 6- and 9-month visits to 2.6 mg/mL and increased to 3.8 mg/ml after the 12-month visit ($p = 0.04$ between visits at 6, 9 and 12 months). The final PC_{20} was not significantly different from the baseline value ($p > 0.05$). In the FP group, PC_{20} increased from 3.9 mg/mL at baseline to 7.9 mg/mL after the 3-month visit ($p < 0.0001$). It kept on increasing during the maintenance period up to 14.5 mg/mL at the 12-month visit ($p = 0.27$). Consequently, the FP group final PC_{20} was higher than the one observed at baseline and also higher than the final PC_{20} of the placebo group ($p = 0.0004$).

When the variations in AHR were expressed in change in doubling PC_{20} values,[37] the FP-treated group and the placebo group improved by 1.14 and 0.27 doubling concentrations respectively, at the 3-month visit ($p = 0.03$, Fig. 3). During the maintenance treatment, in the placebo group, PC_{20} fluctuated by around 0.5 doubling concentrations from baseline ($p > 0.05$) while in the FP group, it went up by 2.16 doubling concentrations compared to baseline value, providing an additional improvement of more than one doubling concentration during the maintenance period compared with the end of the 250 μg/day treatment period.

Airway inflammation during treatments

Total number of cells in induced sputum was unchanged after the 3-, 6-, 9- and 12-month visits in both groups and remained similar between groups (data not shown, $p = 0.39$). At the 3-month visit, the mean percentage of eosinophils decreased from 1.3% to 0.3% ($p = 0.0002$) in the FP group while it did not significantly change in the placebo group: 1.7—1.8% ($p > 0.05$, Fig. 4). At the 6-, 9- and 12-month visits, there were no significant differences compared with baseline sputum eosinophils within groups ($p > 0.05$). However, at the 6- and 9-month visits, mean eosinophil counts were significantly lower in the FP group compared with the placebo group (both $p = 0.02$). At the 12-month visit, all subjects were out of pollen season and eosinophil counts were low in both groups ($p > 0.05$).

Symptoms and PEF after treatments

Compared with baseline, respiratory symptoms did not change significantly in the placebo (0.5 ± 0.7) and the FP (0.3 ± 0.2) groups after the first treatment ($p > 0.05$) and the maintenance treatment ($p > 0.05$; placebo: 0.3 ± 0.6, 0.3 ± 0.6 and 0.2 ± 0.2 respectively; FP: 0.3 ± 0.3, 0.4 ± 0.4 and 0.1 ± 0.2).

Mean AM/PM PEF (% of predicted values) were not significantly different from baseline ($p > 0.05$) in both the placebo and FP groups, after first treatment (Placebo: 83/81 respectively and FP: 89%/88%) and the 6-, 9- and 12-month visits (Placebo: 83/83, 85/83, 88/86 and FP: 90/93, 90/90, 92/90).

Table 2 Adjusted means[a] and 95% CI for PC_{20} methacholine, FEV_1, FEV_1/FVC and sputum eosinophils.

	Placebo group				FP[b] group			
	PC_{20} (mg/mL)	FEV_1 (% predicted)	Ratio FEV_1/FVC (%)	Sputum eosinophils (%)	PC_{20} (mg/mL)	FEV_1 (% predicted)	Ratio FEV_1/FVC (%)	Sputum eosinophils (%)
Baseline	3.2 (2.7–5.6)	98.5 (94.2–102.8)	82.3 (79.8–84.8)	1.7 (1.1–2.5)	3.9 (2.7–5.6)	97.2 (92.7–101.6)	84.2 (82.0–86.3)	1.3 (0.2–3.2)
Visit 3								
3 months post-treatment	4.2 (2.9–6.0)	101.2 (98.6–103.7)	83.6 (82.5–84.8)	1.8 (0.9–3.0)	7.9 (5.2–12.2)	102.9 (99.8–105.9)	85.0 (83.7–86.3)	0.3 (0–1.0)
Visit 4								
6 months post-treatment	2.6 (1.7–3.8)	98.8 (95.9–101.6)	83.0 (81.8–84.3)	2.8 (1.4–4.6)	10.9 (6.9–17.1)	103.1 (99.8–106.2)	85.1 (83.6–86.5)	0.7 (0.1–1.7)
Visit 5								
9 months post-treatment	2.6 (1.7–3.9)	99.6 (96.5–102.7)	82.9 (81.6–84.3)	3.5 (2.0–5.5)	11.1 (6.8–18.3)	104.3 (100.7–107.8)	85.9 (84.3–87.4)	0.8 (0.1–1.9)
Visit 6								
12 months post-treatment	3.8 (2.4–6.0)	100.1 (96.8–103.5)	83.4 (82.0–84.9)	1.6 (0.5–3.2)	14.5 (8.4–25.1)	104.8 (100.8–108.7)	85.5 (83.8–87.2)	0.5 (0–1.6)

[a] Means adjusted for baseline values.
[b] Fluticasone propionate.

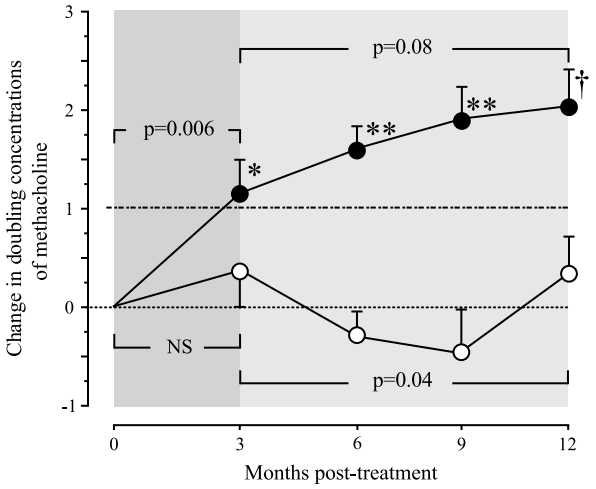

Figure 3 Mean changes (sem) in doubling concentrations of methacholine after treatment (dark shade background), and during maintenance treatment (light shade background) in the placebo (blank circle) and the FP (dark circle) groups. The improvement in number of doubling concentrations was significant in the FP group after treatment ($p = 0.006$). Compared with placebo at each visit: *$p = 0.03$, **$p < 0.0001$, †$p = 0.0004$.

Discussion

Initiating ICS treatment with a high dose, then reducing to the minimum (step-down) has been suggested in asthma although treatment may also be initiated with a low dose then increased if asthma is still uncontrolled.[3,7,38,39] This study showed that a minimal dose of 100 μg/day of FP, maintained the significant improvement in AHR and reduction in airway inflammation obtained after a 3-month treatment with a low dose of 250 μg/day of FP in mild asthma. After 9 months of maintenance treatment with this minimal dose, airway responsiveness and FEV_1 were still improved compared to the placebo group and sputum eosinophils remained in the normal range.

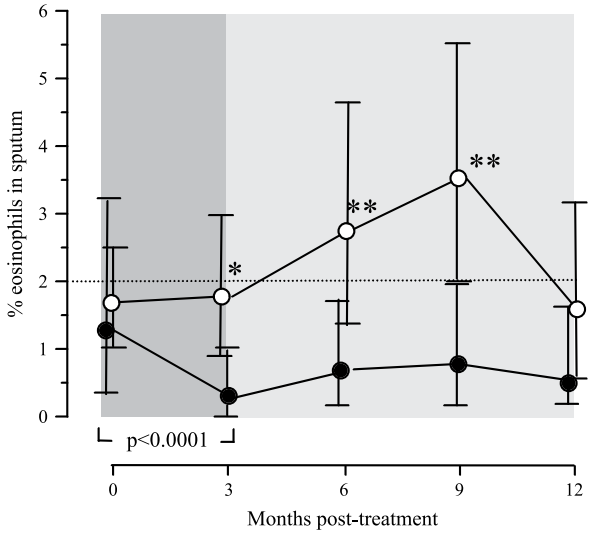

Figure 4 Adjusted mean sputum eosinophil counts (95% CI) before and after treatment (dark shade background), and maintenance treatment (light shade background) in the placebo- (blank circle) and the FP-treated (dark circle) groups. Treatment with FP reduced sputum eosinophils compared with baseline ($p < 0.0001$). Compared with placebo at each visit: *$p = 0.0002$, **$p = 0.02$. Measures from 3 to 12 months adjusted for baseline values.

The fact that FEV_1 and FVC were in the normal range at baseline may explain the small change in lung function after ICS and lack of statistical significance compared to other studies.[40,41] Patients' asthma symptoms scores and PEF measures following FP low-dose treatment and maintenance period remained similar to baseline. The possibility that symptoms were present but not recognized is very unlikely since our patients were good perceivers as confirmed by a perception score of light to moderate symptoms for a 20% decrease in FEV_1 on the first methacholine test.[42] The fact that our patients had mild asthma, few symptoms and normal baseline PEF may explain this apparent lack of effect of treatment on these parameters. In subjects with moderate asthma, doses of 50 and 200 μg/day of FP were efficient to improve FEV_1, AM PEF and reduce asthma symptoms.[40,43] A dose of budesonide equivalent to 125 μg/day of FP also improved lung function and reduced symptoms and risks of severe exacerbations in corticosteroid-naïve patients with moderate asthma.[4]

Adjustments of therapy with ICS by relying on measures of AHR or by assessing sputum eosinophils help to maintain adequate asthma control, especially in reducing the risks of asthma exacerbation.[44–46] However, a controversy exists whether to maintain or stop low-dose ICS when patients with mild persistent asthma become asymptomatic.[8,15,18,47–49] In patients taking ICS, current guidelines, recommend regular therapy with ICS in keeping with the OPTIMA and the START trials while *Boushey et al*. suggested a similar effect of intermittent use of ICS together with an action plan to control asthma exacerbations.[4,6,12,15,22] However, a transient improvement in airway responsiveness and reduction in airway inflammation after short-term treatment with ICS followed by a loss of these benefits over the next few weeks after cessation of treatment has been often observed in subjects with mild to moderate asthma.[3,4,39,44,45,50,51]

Another recent study in which corticosteroid-naïve patients with asymptomatic airway hyperresponsiveness received a high dose of fluticasone for 6 weeks, showed that the beneficial effects of the treatment on airway responsiveness were no longer evident two weeks after cessation of the ICS.[52] In this last study, subjects did not reach a plateau of improvement of airway responsiveness and it is unknown if a treatment prolonged over the 6-week period would have provided further benefits. The loss of beneficial effect after cessation of treatment is also true for sputum eosinophil counts, their increase being a predictor of loss of asthma control and risk of exacerbations.[3,38,51,53] As long-term use of low doses of ICS has minimal adverse effects on child growth and on bone mineral density in adults, this could be considered a safe and effective treatment strategy for both populations.[54–56] Our study further documents the benefits of pursuing a minimal dose of ICS to maintain the improvement obtained with a low dose of ICS in mild asthma.

In these patients, the reduction of sputum eosinophils and their maintenance within the normal range may reduce the risks of clinical exacerbations[3,57–61] and possibly the risk of airway remodelling.[62] Regular maintenance treatment has been shown to be beneficial in patients with mild persistent asthma.[25] This is supported by the demonstration that a 3-year treatment with 400 μg/day of budesonide improved asthma control and reduced asthma exacerbations in adults not previously using regular glucocorticosteroids.[12] As a dose of 250 μg/day of FP followed by a maintenance dose of 100 μg/day of FP was efficient to improve and maintain sputum eosinophils in the normal range and to improve significantly airway responsiveness in patients with mild asthma, we suggest that, in these patients, especially those with a high risk of aggravating their asthma, a prolonged treatment with ICS, at a low dose (the lowest currently recommended in guidelines) is a valuable asthma preventative treatment, minimizing airway hyperresponsiveness and keeping induced sputum eosinophils within the normal range in most patients.

Conflict of interest and financial disclosure statement

LPB: Advisory Boards: AstraZeneca, GlaxoSmithKline, Novartis and Schering-Plough.

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