

Time to onset of effect of fluticasone propionate in patients with asthma

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Background: The effectiveness of inhaled glucocorticoids in the treatment of asthma is well documented; however, times to onset and maximal treatment effects of these agents have been poorly described.

Objective: We sought to determine the time to onset of effect and the time to the best observed effect of inhaled fluticasone propionate (FP) in patients with asthma.

Methods: Data from 8 randomized, double-blind, placebo-controlled clinical trials of at least 8 weeks' duration were analyzed. Corticosteroid-naïve patients (n = 1461) were treated with either FP (25 µg to 500 µg) or placebo twice daily. Efficacy evaluations included morning peak expiratory flow (PEF), asthma symptom scores, supplemental albuterol use, and FEV₁.

Results: Statistically significant improvements in PEF, asthma symptom scores, and supplemental albuterol use were observed beginning on day 1 of treatment in the FP group versus the placebo group ($P < .001$); significant increases in FEV₁ were observed at the first measurement at week 1 ($P < .001$). The best observed effect occurred within 3 weeks of the start of FP treatment for PEF (+36 L/min) and FEV₁ (+0.52 L) and within 2 weeks for reduction in supplemental albuterol use and asthma symptom scores. Patients with the most severe airflow obstruction had the greatest change in PEF (+56 L/min) and fastest time to 50% of best observed effect (3 days) compared with patients with mild or moderate airflow obstruction; however, time to best observed effect was similar in the 3 groups (20 to 27 days).

Conclusion: In patients with asthma, the onset of significant benefit of FP on PEF, symptoms, and rescue albuterol use occurred within 1 day of the start of therapy. FEV₁ improved within 1 week of the start of therapy (the first measurement after randomization). There was no effect of sex, age, or dose of FP on the time to response. The best observed response in PEF varies with the degree of baseline airflow obstruction; however, the degree of airflow obstruction has no effect on the time to best observed response. (*J Allergy Clin Immunol* 1999;103:780-8.)

Key words: Fluticasone propionate, asthma, glucocorticoid, onset, peak expiratory flow, FEV₁

Inhaled glucocorticoids are widely recognized as a highly effective treatment in controlling the symptoms of asthma, as well as the underlying inflammatory process. Clinical actions of inhaled glucocorticoids include reduction in symptom severity, improvement in peak expiratory flow (PEF), reduction of airway responsiveness, and prevention of exacerbations.¹ The time to onset and time to maximal effect of inhaled glucocorticoids, although known to be longer than that of bronchodilator agents (eg, short- or long-acting inhaled β_2 -agonists),¹ is still poorly described, and it is often difficult to determine when there will be a significant benefit to the patient. Additionally, delay in onset of effect with inhaled corticosteroids may have an effect on patient compliance because unlike bronchodilators, the patient may not perceive benefits for several days to weeks of treatment. Thus knowledge of when inhaled corticosteroids begin to exert an effect would be useful for informing patients about how quickly they can expect to obtain clinical benefit and could also be used to determine the optimal duration of a trial of medication before the patient's response is evaluated.

Fluticasone propionate (FP) is an inhaled glucocorticoid currently approved for the maintenance treatment of asthma. It is one of the most topically active corticosteroids developed to date for inhalation therapy in asthma and may provide a faster onset of action than other drugs of its class because of its lipophilicity and high receptor affinity.^{2,3} Inhalation of FP is associated with negligible oral systemic bioavailability, high retention in the lung tissue, low delivery into the serum, and a low risk of systemic adverse effects.³⁻⁸

Patient-to-patient variability makes it difficult to accurately assess the time to onset for inhaled corticosteroids within a single study. The results in this report are based on the retrospective analysis of data contained in a large US database of patients receiving inhaled FP in clinical studies. This database provides a unique opportunity to study time to onset of an inhaled corticosteroid in a large population of patients with asthma evaluated in a rigorously controlled setting. It also provides sufficient numbers of patients to examine response in various demographic and disease subgroups: specifically the effects of age, sex, disease severity, and dose of FP on the time to onset of effect and the time to best observed effect. This analysis was designed to provide a preliminary assess-

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Abbreviations used

FP: Fluticasone propionate
PEF: Peak expiratory flow

ment of whether a general time course for the onset of action of FP could be described and whether a patient's initial response to treatment could be useful in predicting the ultimate magnitude of therapeutic benefit before a lengthy trial of medication.

METHODS

Subjects

All adolescent and adult patients with asthma ($n = 1461$) from a total of 8 randomized, double-blind, placebo-controlled clinical trials of 8 to 12 weeks' duration were included in this analysis. The protocols were approved by the institutional review boards overseeing each respective trial. All patients were corticosteroid naive, were at least 12 years of age, had a diagnosis of asthma as defined by the American Thoracic Society⁹ for at least 6 months, had required therapy for their asthma, had an FEV₁ of 40% to 90% of the predicted value based on Crapo¹⁰ standards for ages 18 years and older or Polgar¹¹ standards for ages 12 to 17 years, demonstrated FEV₁ reversibility of at least 15%, were not current smokers, and had a less than 10 pack-year history of smoking. Doses of FP (Flovent; Glaxo Wellcome, Research Triangle Park, NC) evaluated in these 8 trials ranged from 25 μ g to 500 μ g twice daily and were administered as either an aerosol or powder formulation. Patients were randomized to a dose of FP without regard to their baseline PEF. Supplemental albuterol was supplied for use as needed to control asthma symptoms; no other asthma medications (eg, theophylline, anticholinergics, or cromolyn) were allowed during the studies.

Because patients in each of the clinical trials kept daily records of PEF, morning PEF was chosen as the primary efficacy parameter for analyzing time to onset of effect. Mini-Wright peak flowmeters were used in all of the studies included in this analysis, and predicted peak flows were calculated for each patient by using a nomogram developed for this device.¹² Secondary evaluations of efficacy included FEV₁, supplemental albuterol use, and patient-rated asthma symptom scores. FEV₁ was measured at the clinic at baseline and before the morning dose of study medication at weeks 1, 2, 3, 4, 6, and 8 in all studies, except for one study in which no week 3 measurement was taken. Patients were to withhold supplemental albuterol for at least 6 hours before testing. Supplemental albuterol use (puffs/day) and asthma symptom scores were calculated from daily patient diary records. Asthma symptoms were scored according to the following 4-point scale: 0, none; 1, mild or transient symptoms that may or may not be annoying but caused little or no discomfort; 2, moderate or frequent symptoms that caused discomfort and interfered at least once with normal activities; and 3, symptoms that are continuous and that interfere with activities, sleep, or both.

Data from the 8 controlled clinical trials underwent subgroup analysis to evaluate the possible variables affecting time to onset and best observed effect (ie, age, sex, severity of airway obstruction, and dose). Severity of airway obstruction was categorized according to percent of predicted PEF at baseline, with mild obstruction defined as at least 81%, moderate as 60% to 80%, and severe as less than 60% PEF. Dose response was examined by dividing patients into subgroups receiving nominal doses of 100 μ g or less and of 250 μ g or more FP twice daily. This grouping was based on the fact that 100 μ g twice daily is the current recommended starting dose,

whereas doses of 250 μ g and above are reserved for patients with more severe disease.

Statistical analyses

All summaries and analyses were performed using SAS statistical software. Probability (P) values of .05 or less were considered statistically significant. No P value adjustment for multiple comparisons was performed.

To assist with the interpretation and understanding of the findings outlined in this article, statistical testing was performed on the combined data from 8 distinct protocols. Because the data are derived from 8 different trials, strict statistical interpretation of the P values provided is not possible. The similarities among these studies, however, are extensive. All trials were randomized, parallel, double-blind, and placebo-controlled, involving twice daily treatment with FP, and all included at least 8 weeks of treatment. All subjects included were steroid-naïve asthmatic patients at least 12 years of age. All studies included males and females, and the inclusion and exclusion criteria were similar. In all trials daily diary card assessments, including patient-recorded morning PEF measurements, were collected. All trials started with weekly clinic visits and concluded with biweekly visits. To reduce the risk of bias induced by differences among trials, a term controlling for protocol was included in all statistical procedures.

Baseline values for diary card data (morning PEF, supplemental albuterol use, and asthma symptom scores) were calculated by taking the average of the 7 days immediately before the first dose of study medication. Baseline values for actual and percent of predicted PEF were analyzed by using ANOVA F tests controlling for protocol. All on-treatment efficacy data were summarized as change from baseline; in addition, PEF and FEV₁ were summarized as percent of predicted values. Changes from baseline for all parameters were compared by using ANOVA F tests, controlling for protocol.

Change from baseline for each parameter was calculated for each patient at each day before averaging by group. Because of the variability of PEF measurements, the "best observed" response for PEF was defined as the average PEF for the treatment group during the last 2 weeks of the 8-week study period. Time to onset of effect was defined as the point at which a statistically significant difference in response was detected between the placebo and FP treatment groups. Thus the time to onset of effect and time to best observed response were obtained for the treatment group and not for individual patients. For subgroup analyses, the times to reach 50% and 90% of the best observed response in 8 weeks were used to make comparisons among the groups.

The number of patients withdrawn from the study before completing 8 weeks of treatment was compared between groups by using a Cochran-Mantel-Haenszel test (a chi-squared test controlling for protocol). For patients withdrawn prematurely, the last non-missing value was carried forward in the analyses of efficacy (last observation carried forward analysis).

RESULTS

Demographics

A total of 992 patients received FP and 469 received placebo in the 8 clinical trials. Demographic and baseline disease characteristics were similar in the 2 treatment groups (Table I). Percent of predicted PEF and FEV₁ values were approximately 76% and 66%, respectively, in both groups at baseline. The percentage of patients withdrawn for any reason during the first 8 weeks of the trials was significantly higher in the placebo group than in the FP group ($P < .001$). There were no significant dif-

TABLE I. Baseline demographic and disease characteristics

	FP (n = 992)	Placebo (n = 469)
Sex		
F	369 (37%)	172 (37%)
M	623 (63%)	297 (63%)
Ethnic origin		
Black	52 (5%)	28 (6%)
Hispanic	42 (4%)	27 (6%)
White	880 (89%)	403 (86%)
Other	18 (2%)	11 (2%)
Age (y)*	29.6 ± 12.3 (range, 12-75)	30.1 ± 12.7 (range, 12-78)
PEF (L/min)†		
Baseline	423.3 ± 2.9	417.0 ± 4.1
Percent of predicted	76.4 ± 0.4	75.5 ± 0.6
FEV ₁ (L)†		
Baseline	2.57 ± 0.02	2.53 ± 0.03
Percent of predicted	66.6 ± 0.3	66.4 ± 0.4
Daily number of puffs of supplemental albuterol†	3.5 ± 0.10	3.8 ± 0.15
Asthma symptom score†‡	1.1 ± 0.02	1.1 ± 0.03

*Data represented as mean ± SD.

†Data represented as mean ± SEM.

‡Asthma symptom scores according to the following scale: 0, none; 1, mild or transient symptoms that may or may not be annoying but caused little or no discomfort; 2, moderate or frequent symptoms that caused discomfort and interfered at least once with normal activities; and 3, symptoms that are continuous and that interfere with activities, sleep, or both.

ferences in demographic characteristics among the patients when they were grouped according to dose received (Table II) or sex (data not shown). Baseline PEF and percent of predicted PEF were used to categorize the degree of airflow obstruction (mild, >80% predicted PEF; moderate, 60% to 80%; and severe, <60%). Baseline FEV₁ values and percent of predicted FEV₁ values were significantly different among patients in the mild, moderate, and severe groups ($P < .001$; Table II).

FP versus placebo

Morning PEF. Percent predicted morning PEF at baseline was similar in the FP and placebo treatment groups. The change in PEF from baseline to the best observed value (the average of the last 2 weeks of treatment) was significantly greater in the FP treatment group (36.2 L/min) compared with the placebo group, which did not show a notable improvement (1.9 L/min; $P < .001$). Compared with the placebo group, the mean change in PEF from baseline was significantly greater in the FP group as early as day 1 of treatment ($P < .001$; Fig 1), and significance was maintained throughout the entire treatment period.

The time to reach 50% of the best observed effect in the FP treatment group was less than 1 week, with the time to reach 90% of the best observed response during the 8 treatment weeks occurring approximately 3 weeks from the start of treatment (Table III).

FEV₁, asthma symptom scores, supplemental β -agonist use. Treatment with FP resulted in significant

improvements in FEV₁, asthma symptom scores, and supplemental albuterol use compared with treatment with placebo ($P < .001$) (Figs 2 and 3). Improvement in FEV₁ to within 50% of the best observed effect was shown at the first postbaseline measurement (at 1 week; $P < .001$), and improvement to within 90% of the best observed response occurred within 3 weeks (Table III).

Significant improvement in asthma symptoms was evident after 1 day of treatment ($P < .001$; Fig 3), and 90% of the best observed effect was reached within 2 weeks. A significant decrease in supplemental albuterol use in the FP treatment group versus the placebo group was also noted at day 1 ($P < .001$). The reduction in the number of puffs per day of albuterol reached 50% of the best observed effect after 2 days of treatment with FP, and the best observed effect was reached within 2 weeks of treatment (Fig 3).

Effects on PEF by patient subgroup and dose

Sex and age. There were no significant differences between males and females in time to onset of effect or best observed effect for morning PEF in response to FP treatment (data not shown). Percent predicted PEF increased from 77.0% at baseline to 83.3% after treatment in males and from 75.3% to 82.2% in females.

There were no significant trends with age in time to onset of effect or best observed effect in response to FP among the age categories of 12 to 17, 18 to 50, or 51 or greater years. Changes from baseline in morning PEF for these groups ranged from 26.5 to 39.1 L/min.

Dose of FP. No significant differences were noted in the magnitude of change in morning PEF in response to treatment in patients receiving higher (≥ 250 μ g twice daily) or lower (≤ 100 μ g twice daily) doses of FP (Table IV). Time to reach 50% of the best observed effect was longer in the higher dose group (7 days) than in the lower dose group (4 days); there was no notable difference in time to the best observed effect between the higher and lower dose groups (approximately 3 weeks). There was no evidence of dose response when higher and lower doses were analyzed within each of the 3 severity groups (data not shown).

Degree of airflow obstruction. When analyzed by baseline airflow obstruction, the magnitude of change in morning PEF in response to FP treatment was significantly greater in patients with severe obstruction at baseline and smallest in those patients with the mildest disease ($P < .001$; Table IV). Significant improvement from baseline in PEF was seen in all severity groups within 1 day of treatment ($P < .001$). Patients with severe obstruction showed the most rapid improvement: 3 days to reach 50% of the best observed response compared with 5 days and 7 days in patients with moderate and mild obstruction, respectively. The time to reach 90% of the best observed response was approximately 3 weeks for patients with moderate or severe airflow obstruction and approximately 4 weeks for patients with mild obstruction. However, the best observed percent predicted PEF

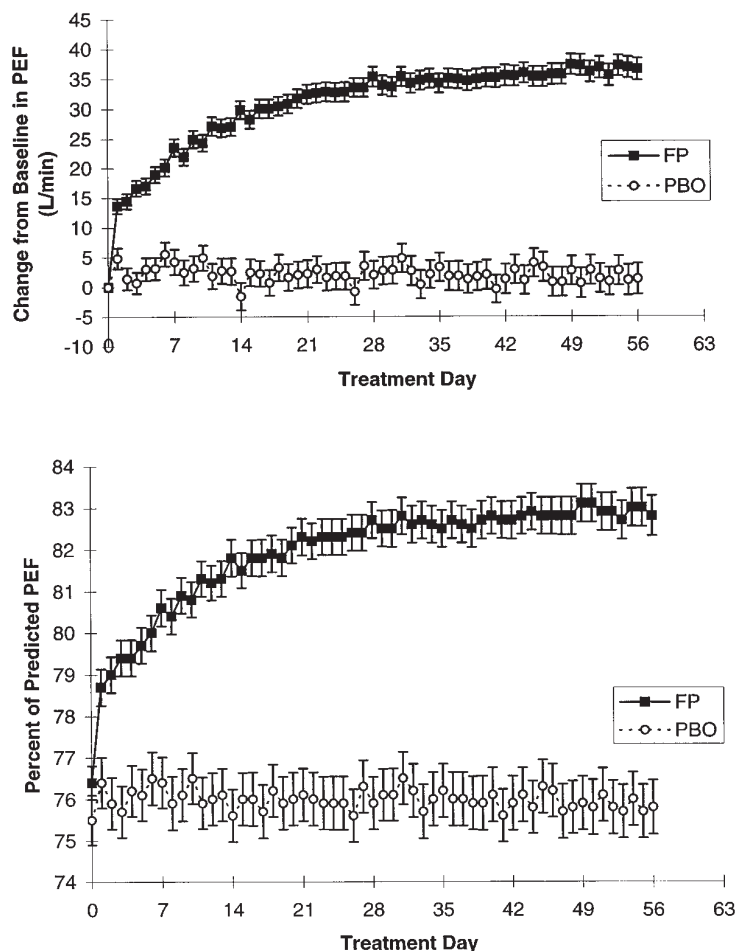


FIG 1. Change from baseline in PEF (L/min) and percent of predicted PEF (%) in the FP and placebo treatment groups. $P < .001$ for all time points. *PBO*, Placebo.

TABLE II. Baseline characteristics by patient subgroup

	Dose of FP (twice daily)		Baseline airflow obstruction		
	$\leq 100 \mu\text{g}$ (n = 744)	$\geq 250 \mu\text{g}$ (n = 248)	Mild (n = 390)	Moderate (n = 475)	Severe (n = 127)
Sex					
F	274 (37%)	95 (38%)	144 (37%)	161 (34%)	64 (50%)
M	470 (63%)	153 (62%)	246 (63%)	314 (66%)	63 (50%)
Ethnic origin					
Black	36 (5%)	16 (6%)	18 (5%)	26 (5%)	8 (6%)
Hispanic	24 (3%)	18 (7%)	21 (5%)	14 (3%)	7 (6%)
White	672 (90%)	208 (84%)	344 (88%)	427 (90%)	109 (86%)
Other	12 (2%)	6 (2%)	7 (2%)	8 (2%)	3 (2%)
Age (y)*	29.3 $\pm$ 12.6 (range, 12-75)	30.5 $\pm$ 11.5 (range, 12-62)	28.1 $\pm$ 11.4 (range, 12-74)	29.4 $\pm$ 12.3 (range, 12-69)	35.2 $\pm$ 13.9 (range, 12-75)
PEF (L/min) [†]					
Baseline	419.4 $\pm$ 3.5	435.2 $\pm$ 5.6	494.3 $\pm$ 3.6	400.7 $\pm$ 2.8	290.1 $\pm$ 4.7‡
Percent of predicted	75.8 $\pm$ 0.5	78.1 $\pm$ 0.8	88.9 $\pm$ 0.3	71.9 $\pm$ 0.2	54.5 $\pm$ 0.5‡
FEV ₁ (L) [†]					
Baseline	2.6 $\pm$ 0.02	2.6 $\pm$ 0.04	2.8 $\pm$ 0.03	2.5 $\pm$ 0.03	2.1 $\pm$ 0.05
Percent of predicted	66.6 $\pm$ 0.4	66.8 $\pm$ 0.5	70.3 $\pm$ 0.5	65.0 $\pm$ 0.4	61.4 $\pm$ 0.8
Daily number of puffs of supplemental albuterol [†]	3.7 $\pm$ 0.11	3.1 $\pm$ 0.18	3.0 $\pm$ 0.15	3.7 $\pm$ 0.14	4.2 $\pm$ 0.28

*Data represented as mean $\pm$ SD.

[†]Data represented as mean $\pm$ SEM.

[‡]For differences in baseline asthma severity groups, $P < .001$ based on an ANOVA F test controlling for protocol.

TABLE III. Time to onset and best observed effect

	Treatment group		P value
	FP	Placebo	
PEF			
n	992	469	—
Mean best observed change	36.2 L/min (9.5%)	1.9 L/min (0.5%)	<.001
Time to 50% of best observed effect	5 days	—	—
Time to 90% of best observed effect	22 days	—	—
FEV ₁			
n	948	422	—
Mean best observed change	0.52 L (20.2%)	0.19 L (7.5%)	<.001
Time to 50% of best observed effect	<1 week	—	—
Time to 90% of best observed effect	<3 weeks	—	—
Symptom scores			
n	991	469	—
Mean best observed change	−0.40 (−36%)	−0.09 (−8.2%)	<.001
Time to 50% of best observed effect	1 day	—	—
Time to 90% of best observed effect	14 days	—	—
Albuterol use			
n	875	358	—
Best observed change	−1.61 puffs/day (−46%)	−0.13 puffs/day (−3.4%)	<.001
Time to 50% of best observed effect	2 days	—	—
Time to 90% of best observed effect	14 days	—	—
Number of patients withdrawn prematurely (for any reason)	186 (19%)	162 (35%)	<.001

All data are expressed as means (percent change from baseline), except for withdrawals. Time to 50% and 90% of the best observed effect were not computed for the placebo treatment group because of the lack of significant change in this group of patients.

in patients with severe obstruction (65.0%) remained far below that of patients with mild (93.0%) or moderate (79.4%) obstruction after treatment (Fig 4).

DISCUSSION

In this analysis of data from 8 randomized, double-blind, placebo-controlled clinical trials, statistically significant responses to FP treatment, as assessed by morning PEF, asthma symptom scores, and reduction in supplemental albuterol use, were evident within 1 day of beginning therapy. The current results are consistent with previously published analyses based on a subset of the earlier individual trials in this database.^{13,14} The time to reach 50% of the best observed response in 8 weeks in the FP treatment group, as evidenced by a significant reduction in patient-rated asthma symptom scores and supplemental albuterol use, was observed after 1 to 2 days of treatment, preceding the corresponding changes in PEF (5 days). The best observed effect during the 8 weeks of therapy occurred within approximately 3 weeks of FP treatment for PEF and FEV₁ and within 2 weeks of treatment for asthma symptom scores and reduction in supplemental albuterol therapy.

No differences in time to best observed effect or time to onset of effect for PEF were noted between males and females or among different age categories. There was no evidence of a dose response in time to onset or best observed response with FP in asthmatic patients treated with as-needed bronchodilators at baseline, which is consistent with previous reports.^{5,6} These results suggest that higher doses of FP do not necessarily lead to a quicker

response or greater improvement. The lack of a dose response was also seen in the patients with the most severe airflow obstruction; in contrast, another study has shown a dose-dependent improvement in FEV₁ and a decrease in the need for oral prednisone in patients receiving higher doses of FP for severe asthma.¹⁵ It should be noted that none of the clinical trials included in this analysis was powered to detect differences in response between FP dose groups but only between FP and placebo. These clinical trials were conducted in patients with less severe asthma, for which the lowest doses of FP have been shown to be highly effective. Also, patients in the higher dose group had a slightly higher than average baseline PEF value than those in the lower dose group, which could have an impact on any possible dose-response analyses.

Although those patients with the most severe airway obstruction (baseline PEF, ≤60% of predicted value) had the greatest magnitude of improvement in morning PEF, they still did not achieve the level of lung function observed in patients with mild or moderate airway obstruction (Fig 4). This failure of the most severely afflicted patients to obtain a level of lung function as high as that seen in patients with mild or moderate obstruction may be a result of pathophysiologic changes of their disease (ie, lung remodeling) that can occur because of inadequately treated inflammation over time and may also be related to the duration of asthma in these patients,¹⁶ although there is some evidence that lung remodeling may be more indicative of the severity of disease rather than the duration of asthma.¹⁷ In addition, these results may be due to the fact that in this study

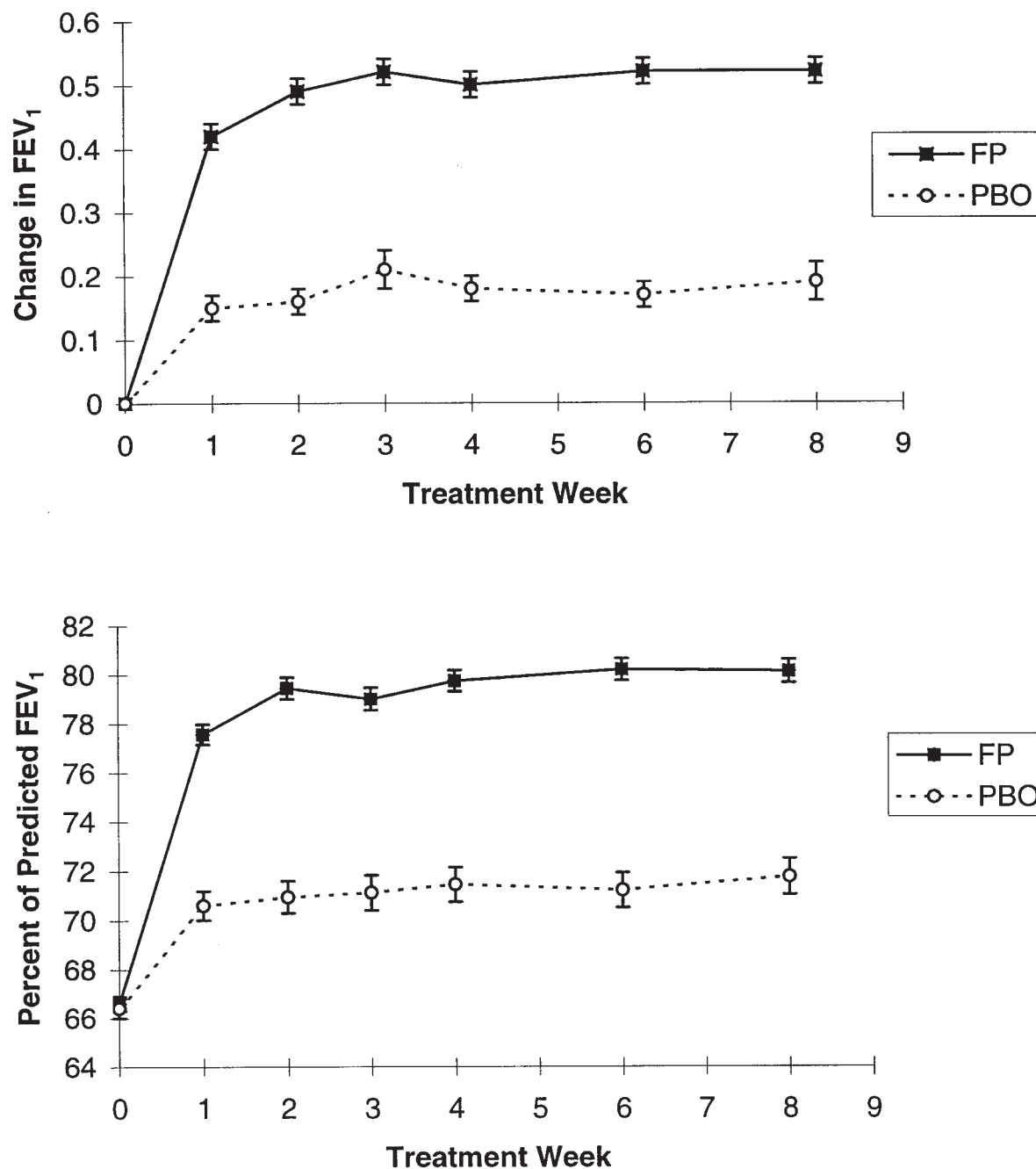


FIG 2. Change from baseline in FEV₁ (L) and percent of predicted FEV₁ (%) in the FP and placebo treatment groups. Only 7 of the 8 clinical trials included in the analysis collected FEV₁ data at week 3. $P < .001$ for all time points. PBO, Placebo.

patients were categorized on the basis of airflow obstruction as defined by PEF, which may have produced selection bias (eg, smaller lung size in one group). The current analyses were not designed to address these issues (response vs severity), and therefore the reasons for the observed findings remain speculative. This study has also shown that regardless of how large the best observed improvement in morning PEF, across categories of sever-

ity of airway obstruction patients tended to achieve this improvement on the same general time course; that is, onset of significant therapeutic effect occurred within 1 day, regardless of baseline severity.

The enrollment criteria of the 8 clinical trials used in these analyses specified that patients were corticosteroid naive and were at least 12 years of age, and the studies excluded patients with the most severe disease (FEV₁

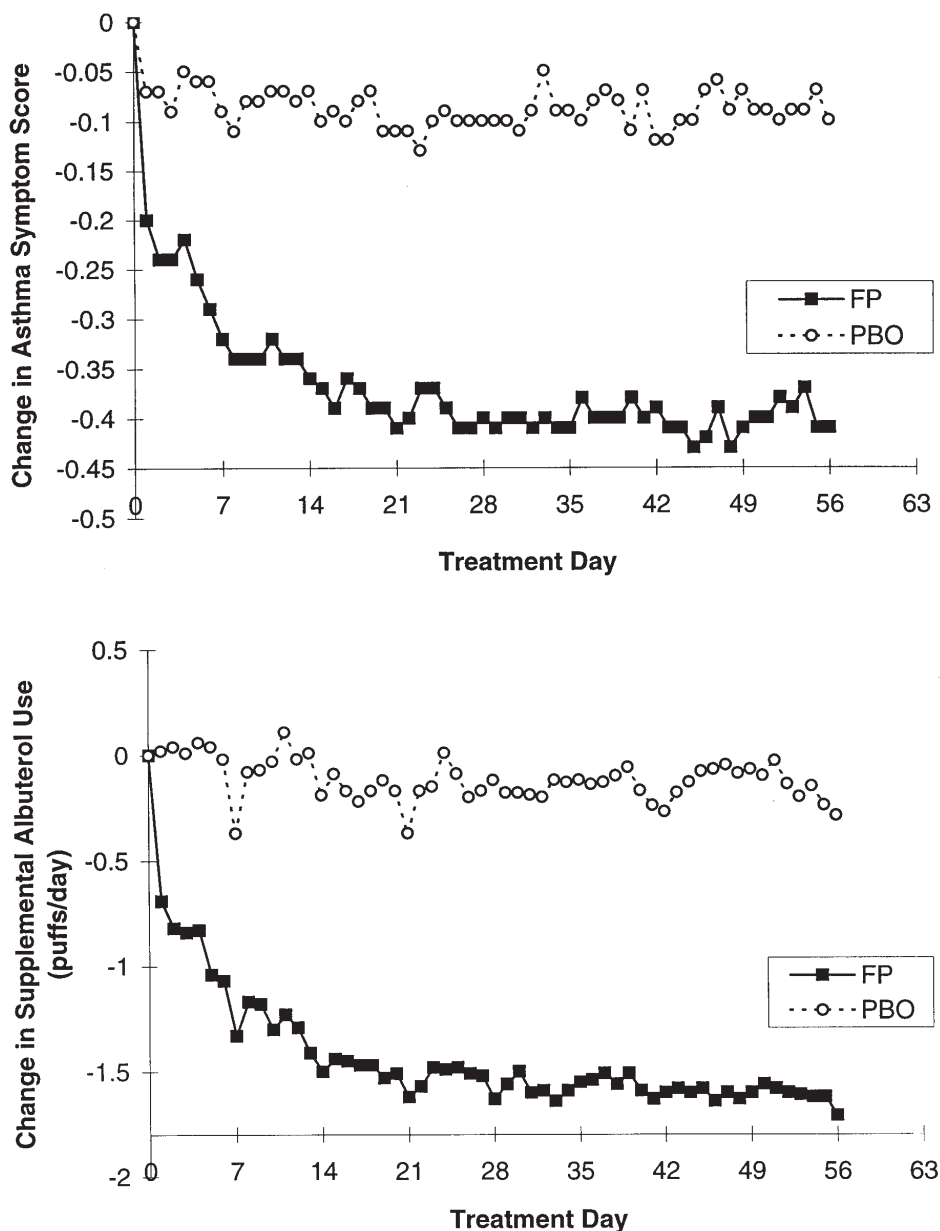


FIG 3. Change from baseline in total asthma symptom score (top) and supplemental albuterol use (bottom) in the FP and placebo treatment groups. $P < .001$ for all time points. PBO, Placebo.

TABLE IV. PEF: Time to onset and best observed effect by dose and airflow obstruction

	Maximum change from baseline (L/min)	Time to 50% effect (days)	Time to 90% of best observed effect (days)
FP dose			
≤100 µg twice daily	36.3	4	23
≥250 µg twice daily	35.9	7	21
Airflow obstruction			
Mild	23.2	7	27
Moderate	41.4	5	20
Severe	56.1	3	22

<40% of predicted value at baseline). Therefore by design this population represents only a subset of patients seen in clinical practice. In addition, the conclusions reported here are based on responses to a single inhaled glucocorticoid and thus should not be taken as a general measure of response for all inhaled corticosteroids. A previous study examining time to onset of response to high doses of oral glucocorticoids in children with severe asthma reported that a significant response (defined as an increase in prebronchodilator FEV₁ of at least 15% over baseline) to treatment occurred within 10 days; the authors recommended that patients who did not respond within 10 days be placed on alternative treat-

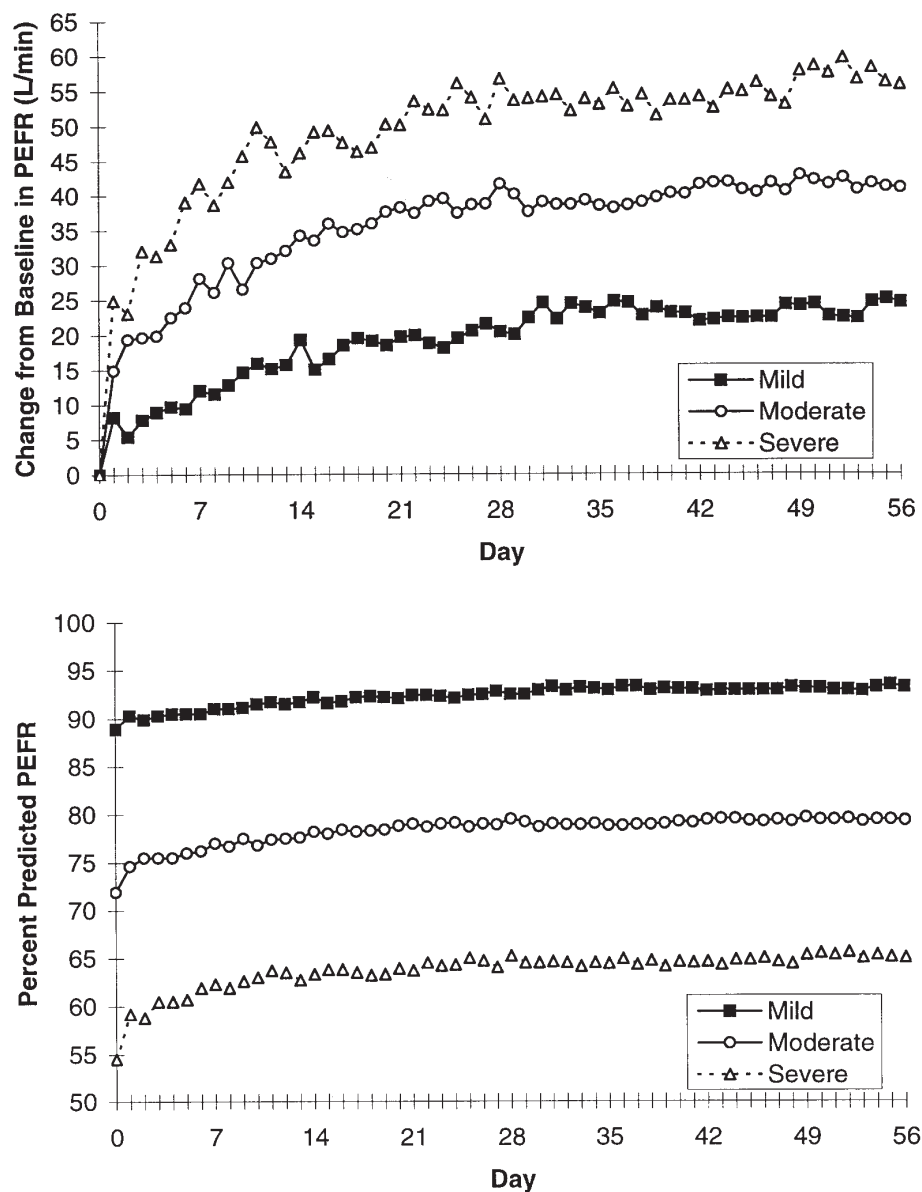


FIG 4. Change from baseline in peak expiratory flow rate (PEFR) and percent of predicted PEFR in patients with mild, moderate, or severe asthma treated with FP. For change from baseline, $P < .001$ for all time points and for all levels of severity.

ment.¹⁸ These results are consistent with those of the current study of inhaled FP in adult patients with asthma. Package labeling for other inhaled corticosteroids indicated for the treatment of asthma state that benefits should be apparent within 1 to 2 or 1 to 4 weeks of starting therapy.¹⁹ However, to our knowledge, there are no other published data outlining in detail the time to onset of significant therapeutic benefit for drugs of this class.

This report represents the first large-scale examination of time to onset of action and maximal effect of FP in patients with asthma. The results of this analysis indicate that the onset of action of FP occurs within 1 day of beginning therapy, and patient-rated scales indicate that significant benefit may be perceived by the first day of

treatment. In addition, near-maximal improvement in lung function parameters and asthma symptoms can be expected within 3 weeks of the initiation of therapy for patients with mild-to-moderate asthma. The relatively fast onset of action of FP, as shown by both objective lung function tests and the patient's subjective perception of asthma symptoms, may lead to improved compliance and therefore better symptom control in patients with asthma requiring corticosteroid therapy.

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